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CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Randomized Phase 3 Study of Tislelizumab in Combination With Sitravatinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody
Protocol Identifier:	BGB-A317-Sitravatinib-301
Phase:	3
Investigational Product(s):	Tislelizumab (BGB-A317) and Sitravatinib (BGB-9468)
Indication:	Locally Advanced or Metastatic Non-Small Cell Lung Cancer
EudraCT Number:	2022-001779-15
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive 3rd Floor San Mateo, CA 94404, USA
Sponsor Medical Monitor:	[redacted]
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FINAL PROTOCOL APPROVAL SHEET

BGB-A317-Sitravatinib-301: A Randomized Phase 3 Study of Tislelizumab in Combination With Sitravatinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody

BeiGene, Ltd., Approval:

[redacted]

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized Phase 3 Study of Tislelizumab in Combination With Sitravatinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody

Protocol Identifier: BGB-A317-Sitravatinib-301

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Instructions for Investigator: Please SIGN and DATE this signature page before implementation of this sponsor-approved protocol. PRINT your name, title, and the name of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Product: Tislelizumab (BGB-A317) and Sitravatinib (BGB-9468)
Title of Study: A Randomized Phase 3 Study of Tislelizumab in Combination With Sitravatinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody
Protocol Identifier: BGB-A317-Sitravatinib-301
Phase of Development: 3
Number of Patients: Approximately 420
Study Centers: Approximately 100 centers globally

Study Objectives:

Primary:

- To compare the overall survival (OS) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy
- To compare the progression-free survival (PFS) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the Independent Review Committee (IRC)

Secondary:

- To compare the PFS of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the investigator
- To compare the overall response rate (ORR), duration of response (DOR), and disease control rate (DCR) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the IRC
- To evaluate the safety and tolerability of tislelizumab and sitravatinib combination therapy compared with that of docetaxel monotherapy
- To evaluate and compare health-related quality of life (HRQoL) between the tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy via patient reported outcomes using EORTC-QLQ-C30 (measuring general cancer) and its lung cancer module, QLQ-LC13, and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)
- To characterize the pharmacokinetics (PK) of sitravatinib when given in combination with tislelizumab, if data permit

Exploratory:

- To compare the combination of tislelizumab with sitravatinib versus docetaxel monotherapy, as measured by ORR, DOR, and DCR assessed by the investigator
- To explore the predictive and prognostic effect of programmed cell death protein ligand-1 (PD-L1) expression level
- To characterize the PK of the active metabolite M10 of sitravatinib when given in combination with tislelizumab, if deemed necessary

- To characterize the PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To explore potential biomarkers that may correlate with clinical responses or resistance to sitravatinib in combination with tislelizumab

Study Endpoints:

Primary:

- OS, defined as the time from randomization to death from any cause
- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRC based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause, whichever occurs first

Secondary:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator based on RECIST v1.1, or death from any cause, whichever occurs first
- ORR, defined as the proportion of patients with partial response or complete response as determined by the IRC based on RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, as determined by the IRC based on RECIST v1.1, or death from any cause, whichever comes first
- DCR, defined as the proportion of patients whose best overall response (BOR) is complete response, partial response or stable disease as determined by the IRC based on RECIST v1.1
- HRQoL, defined as changes in patient-reported outcomes (PRO), according to the European Organisation for Research and Treatment of Cancer (EORTC) core cancer (QLQ-C30) and its lung cancer module, QLQ-LC13, and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) from time of randomization to End of Treatment Visit, death or drop out, whichever comes first.
- Incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0
- Plasma concentrations and the derived PK parameters of sitravatinib if data permit

Exploratory:

- ORR, defined as the proportion of patients with partial response or complete response as determined by the investigator based on RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, as determined by the investigator based on RECIST v1.1, or death from any cause, whichever comes first
- DCR, defined as the proportion of patients whose BOR is complete response, partial response, or stable disease based on RECIST v1.1 by investigator
- To explore the predictive and prognostic effect of PD-L1 expression level on OS
- To evaluate the predictive and prognostic effect of PD-L1 expression level using PFS, ORR,

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and DCR by IRC and investigator

- Plasma concentrations and the derived PK parameters of M10 if data permit
- Serum concentrations of tislelizumab and the incidence of antidrug antibodies (ADAs)
- Potential biomarkers such as PD-L1 expression, gene expression profiling, tissue and blood tumor mutation burden and microsatellite instability, and alterations in tissue and circulating tumor DNA, and the association of biomarkers with disease status, and response/resistance to sitravatinib in combination with tislelizumab.

Study Design:

This is an open-label, randomized, multicenter, Phase 3 clinical study evaluating the efficacy and safety of tislelizumab in combination with sitravatinib compared with docetaxel in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have disease progression following platinum-based chemotherapy and anti-programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy.

Patients must have received no more than 2 lines of prior systemic therapy for locally advanced and unresectable or metastatic disease. In addition, patients must have had radiographic progression per RECIST v1.1 on or after anti-PD-(L)1-containing therapy for locally advanced and unresectable or metastatic NSCLC. If anti-PD-(L)1-containing therapy is not the most recent systemic treatment, patients should also have radiographic progression per RECIST v1.1 on or after the most recent systemic treatment. Adjuvant or neo-adjuvant chemotherapy will be counted as 1 prior line of chemotherapy if the disease progressed on or within 6 months after the completion of the last dose. In locally advanced and unresectable NSCLC, disease progression on or within 6 months after the end of systemic therapy as part of prior curatively intended multimodal therapy will be counted as 1 prior line of systemic therapy. If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course counts as 1 line of therapy (Patients who received anti-PD-[L]1 antibody as consolidation treatment following definitive chemoradiation for unresectable Stage III NSCLC can be enrolled immediately after disease progression, if the disease progression occurred within 6 months after the end of platinum-based chemotherapy component of the definitive chemoradiation). Maintenance therapy following platinum-based chemotherapy is not considered as a separate line of therapy. No other prior immunotherapies with antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, including but not limited to anti-TIGIT, anti-OX40, and anti-CD137, will be allowed (prior anti-cytotoxic T-lymphocyte protein 4 [CTLA-4] used in combination with anti-PD-[L]1 is permitted); no prior anticancer therapy having the same mechanism of action as sitravatinib (eg, tyrosine kinase inhibitor with a similar target profile or VEGF- or VEGFR inhibitor) will be allowed either.

The study will be conducted at approximately 100 centers globally. The study will consist of a screening period, a treatment period, and a long-term follow-up period. Approximately 420 patients with locally advanced or metastatic NSCLC will be enrolled and randomized in a 1:1 ratio to receive either tislelizumab in combination with sitravatinib or docetaxel monotherapy.

Patients with histologically or cytologically confirmed locally advanced or metastatic (Stage IIIB/IIIC or Stage IV) NSCLC who have disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after platinum-based chemotherapy, are eligible. Histology of NSCLC will be confirmed at the investigator's site. Patients with known *EGFR* or *BRAF* sensitizing mutation, or *ALK* or *ROS1* rearrangement are ineligible for the study; for patients with nonsquamous NSCLC without tissue-based *EGFR* status, fresh or archival tumor tissues are required for *EGFR* mutation assessment.

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Archival tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. If archived formalin-fixed paraffin-embedded tissue is not sufficient for PD-L1 analysis, a fresh biopsy sample will need to be obtained. PD-L1 status will be determined by the percentage of tumor cells with any membrane staining (tumor cells [TC]+) above background. Patients will be stratified by histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% TC versus ≥ 1% TC by the Ventana SP263 assay; patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group), and race (Asian versus non-Asian) to receive one of the following treatment regimens:

- Arm A: tislelizumab 200 mg intravenously once every 3 weeks in combination with sitravatinib 100 mg orally once a day
- Arm B: docetaxel 75 mg/m^2 intravenously once every 3 weeks

Cycle 1 Day 1 will be defined as the first day the patient receives the study drug. A cycle is 21 days in length ± 3 days, unless a delay is medically necessary. A ± 3-day window is allowed for protocol-required assessments, unless otherwise specified. Tumor assessment will be conducted (by magnetic resonance imaging and/or computed tomography [with oral and/or intravenous contrast, unless contraindicated]) during screening (within 28 days of Day 1); every 6 weeks from Cycle 1 Day 1 (± 7 days) (at Weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter, until disease progression, withdrawal of consent, lost to follow-up, start of a new anticancer therapy, or death, whichever occurs earlier.

Patients in both arms will receive study treatment until disease progression, intolerable toxicity, death, or withdrawal of consent, whichever occurs earlier.

Patients will not be allowed to cross over to the other treatment arm. Tumor assessment and response will be determined by the IRC, who will evaluate disease progression and responses without the knowledge of randomization assignments, in accordance with RECIST v1.1.

Response and disease progression will be assessed using RECIST v1.1. When disease progression is assessed by the investigator, the IRC is required to complete central image review and convey the results to the investigator as soon as possible. If disease progression is not confirmed by the IRC, it is recommended to continue the study treatment until disease progression is confirmed by the IRC, if this is in the best interest of the patient as discussed with the medical monitor. In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for the IRC's confirmation, the investigator should contact the medical monitor to inform him/her of the decision of treatment discontinuation.

A patient who discontinues study drugs early for reasons other than disease progression as assessed by IRC (eg, toxicity, disease progression assessed by the investigator) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression per RECISTv1.1 as assessed by the IRC, withdraws consent, is lost to follow-up, starts a new anticancer treatment, until death, or until the study terminates, whichever occurs first.

In selected cases, patients in Arm A may continue treatment beyond radiologic progression if they continue to demonstrate clinical benefit, at the discretion of the investigator and with the sponsor's agreement. The following criteria must be met in order to treat patients beyond progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤ 1

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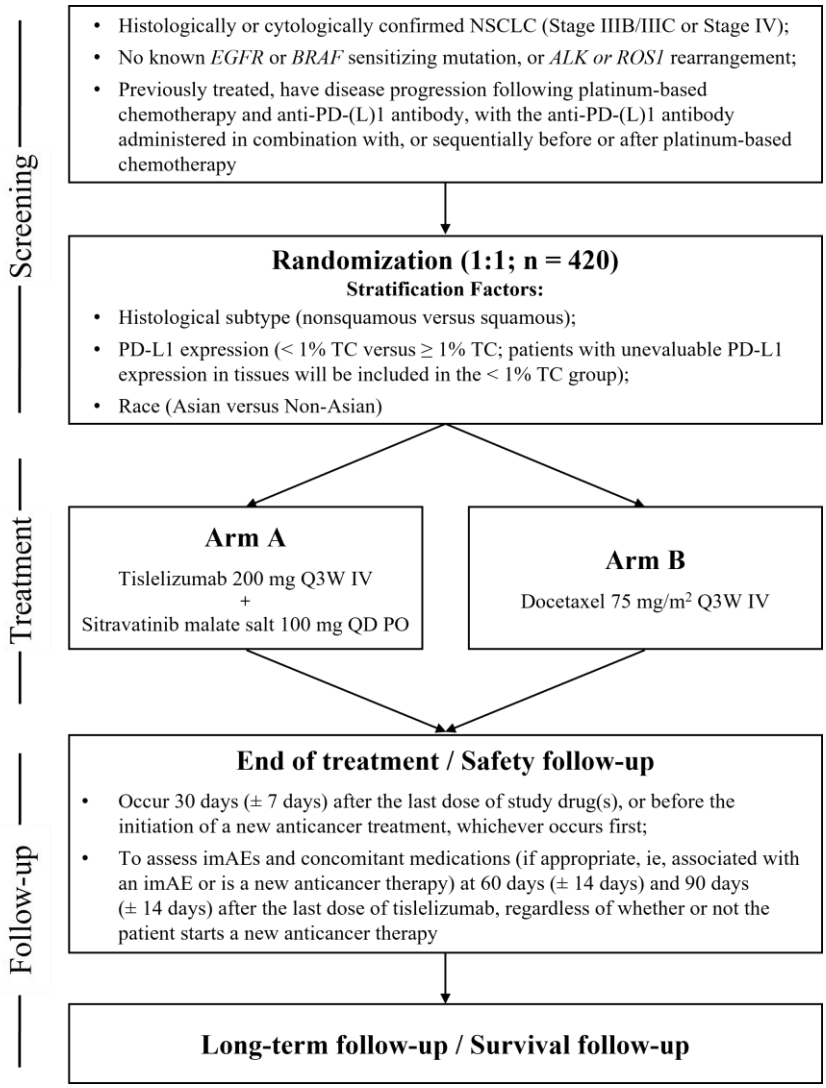
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention

Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

Patients who could benefit from study treatment in Arm A after disease progression as assessed by the investigator or IRC per RECIST v1.1 criteria may continue treatment until loss of clinical benefit as assessed by the investigator, withdrawal of consent, unacceptable toxicity, study completion by the sponsor, start of a new anticancer therapy, or death, whichever occurs first. Tumor assessment should continue as planned in patients receiving study treatment beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

At the end of treatment or after treatment discontinuation, the date of progression, type and duration of subsequent therapies, response to subsequent therapy, date of progression on subsequent therapy, and survival data will be collected.

Study Schema:



Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; imAE, immune mediated adverse event; IV, intravenously; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein-1/programmed cell death protein ligand-1; PO, orally; ROS1, ROS proto oncogene 1; QD, once a day; Q3W: every 3 weeks; TC, tumor cells

Study Assessments:

Study assessments will be described in the schedule of assessments. Patients will be closely monitored for safety and tolerability throughout the study.

Duration of Patient Participation:

The duration of the study from the first enrolled patient to the final analysis for the primary endpoint of OS is estimated to be approximately 32 months.

Study Population:

Approximately 420 patients with locally advanced or metastatic NSCLC who have experienced disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy.

Key Eligibility Criteria:

Adult patients (≥ 18 years of age or the legal age of consent if > 18) with metastatic or unresectable locally advanced histologically or cytologically confirmed NSCLC, who were previously treated with no more than 2 lines of prior systemic chemotherapy and anti-PD-(L)1 antibody therapy are eligible. Patients with known *EGFR* or *BRAF* sensitizing mutation, or *ALK* or *ROS1* rearrangement are ineligible for the study; for patients with nonsquamous NSCLC without tissue-based *EGFR* status, fresh or archival tumor tissues are required for *EGFR* mutation assessment. In addition, archival tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. If archived formalin-fixed paraffin-embedded tissue is not sufficient for PD-L1 analysis, a fresh biopsy sample will need to be obtained. All patients are also required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤ 1 and adequate organ function.

Investigational Product, Dose, and Mode of Administration:

Sitravatinib: Sitravatinib will be administered orally at a dose of 100 mg, once daily continuously. Dosing of sitravatinib can be withheld for up to approximately 28 days consecutively. Generally, A maximum of 2 dose reductions are allowed before the patient must be permanently withdrawn from the study drug. Dose reduction below 50 mg once daily may be undertaken after discussion with the sponsor. If the study drug is planned to be held for > 28 days, the medical monitor should be contacted before the patient is permanently discontinued from the study drug.

The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken on an empty stomach (≥ 2-hour fast before each dose and no food for a minimum of 1 hour after each dose).
- Capsules should be taken with at least 200 mL (approximately 1 cup) of water.
- Patients should swallow the capsules whole and not chew them.
- If vomiting occurs after dosing, sitravatinib doses should not be replaced.
- If a patient forgets to take sitravatinib for more than 12 hours, he/she should skip the dose and

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resume taking the drug the next day.

Tislelizumab: Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks. As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterwards in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents if no symptoms are observed after the prior 2 drug administrations.

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes. If this is well-tolerated, then the subsequent infusions may be administered over 30 minutes if no symptoms are observed during the first treatment administration. Thirty minutes is the shortest time period permissible for infusion of tislelizumab. Tislelizumab must not be concurrently administered with any other drug.

There will be no dose reduction for tislelizumab in this study. Dose delays of ≤ 12 weeks will be permitted. The tumor assessment schedule will not be altered even if the administration of study drug(s) is delayed.

On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib should precede tislelizumab infusion for logistical reasons. This order of dosing is important on days when blood sampling is scheduled for sitravatinib and M10 PK analysis.

In the event of unacceptable AEs potentially attributed to anti-PD-1 therapy and clearly not attributed to RTK inhibitor, sitravatinib can be continued as monotherapy at the discretion of the investigator. However, due to limited anticancer effect of rechallenging PD-(L)1 monotherapy after progression on PD-(L)1 inhibitor or PD-(L)1-inhibitor-based therapy, tislelizumab should not be used as monotherapy after permanent discontinuation of sitravatinib. When attribution to an unacceptable adverse event by either drug cannot be ruled out, both sitravatinib and tislelizumab should be held or the dose of sitravatinib should be reduced according to dose modification guidelines.

Reference Therapy, Dose, and Mode of Administration:

Docetaxel: Docetaxel will be administered every 3 weeks by intravenous infusion at 75 mg/m^2 over 1 hour, or according to institutional practices. Premedication with corticosteroids will be required in accordance with regional standards.

Statistical Methods:

OS and PFS by IRC are dual primary endpoints in this study. The type I error is strongly controlled by initially assigning a 1-sided alpha of 0.001 to the PFS hypothesis and 0.024 to the OS hypothesis. By using the graphic approach of Bretz (2009), if the PFS by IRC or the OS hypotheses are both rejected, the corresponding alpha will be shifted to the hypothesis test of the secondary efficacy endpoints, ORR per RECIST v1.1 assessed by the IRC.

Analysis Sets:

- The Intent-to-Treat Analysis Set includes all randomized patients. It will be the primary analysis set for the efficacy analysis.
- The Safety Analysis Set includes all patients who received ≥ 1 dose of any of the study drugs. It will be the primary analysis set for the safety analysis.
- The Sitravatinib PK Analysis Set includes all patients in the Safety Analysis Set who contributed ≥ 1 quantifiable postbaseline PK sample for sitravatinib.
- The M10 PK Analysis Set includes all patients in the Safety Analysis Set who contributed

≥ 1 quantifiable postbaseline PK sample for M10.

- The Tislelizumab PK Analysis Set includes all patients in the Safety Analysis Set who contributed ≥ 1 quantifiable postbaseline PK sample for tislelizumab.
- The ADA Analysis Set includes all patients who received ≥ 1 dose of tislelizumab and for whom both baseline ADA and ≥ 1 postbaseline ADA result are available.

The final analysis of OS will take place after approximately 289 OS events have been observed.

On the basis of emerging external data, the testing strategy may be modified to improve the efficiency of the design. Should this occur, modifications to the testing strategy will be documented in the statistical analysis plan (SAP) before the unblinding of the study.

Sample Size Considerations:

The sample size calculation is based on the primary efficacy analysis of OS in the Intent-to-Treat Analysis Set. The hazard ratio of OS is assumed to be 0.70, with a median OS of 14.3 months in the treatment arm and 10.0 months in the comparator arm. The dropout rate for OS is assumed to be 5% per year. A total of 420 patients will be enrolled in a 1:1 randomization over an 18-month period, at a maximum enrollment rate of 28 patients/month and a ramp-up period of 6 months. Approximately 289 OS events are planned for the final analysis, to have a power of 85% with an alpha of 0.024. A group sequential testing of OS will be performed. The hazard ratio assumption of PFS is 0.63 with a median PFS of 5.4 months in the treatment arm and 3.4 months in the control arm. Approximately 332 PFS events are expected to occur at the final analysis of PFS, to have a power of 87% with an alpha of 0.001.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
BGB-A317	tislelizumab
BGB-9468	sitravatinib
CR	complete response
CT	computed tomography
DCR	disease control rate
CYP3A4	cytochrome P450 3A4
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture (system)
EOT	End-of-Treatment (Visit)
Fc	fragment crystallizable region (typically, of immunoglobulin G)
FDG	fluorodeoxyglucose
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IB	Investigator's Brochure
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
OS	overall survival

Abbreviation	Definition
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-(L)1	programmed cell death protein-1/programmed cell death protein ligand-1
PFS	progression-free survival
PET	positron emission tomography
PK	pharmacokinetic(s)
PPE	palmar-planta erythrodysesthesia
PR	partial response
PRO	patient -reported outcome
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
TEAE	treatment-emergent adverse event
TC	tumor cells
TME	tumor microenvironment
ULN	upper limit of normal

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1. INTRODUCTION

1.1. Background Information on Non-Small Cell Lung Cancer

Lung cancer is the most common type of cancer occurring in both men and women in the past decades and is the leading cause of cancer deaths worldwide. In 2020, an estimated 228,820 new cases of lung cancer will be diagnosed, and 135,720 deaths are estimated to occur because of the disease in the United Sates (NCCN Guideline Version 1, 2020). Lung cancer is also the most commonly diagnosed lung malignancy and it remains one of the deadliest diseases in China; about 782,000 new cases of lung cancer were diagnosed in 2014 (Chen et al 2015). According to statistics from the National Office on Tumor Cure and Prevention, about 626,000 people die of lung cancer each year in China (Chen et al 2018).

Characterized by uncontrolled growth of abnormal cells in the lung, lung cancer includes 2 major pathological types: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for 80% to 85% of all lung cancers (American Cancer Society 2020). There are 2 main types of NSCLC: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other subtypes) and squamous cell (epidermoid) carcinoma (NCCN Guideline Version 1, 2020).

For several decades, the conventional anticancer strategies have been surgery, chemotherapy, and radiotherapy. The success of immune checkpoint therapy in recent years has revolutionized traditional cancer treatment. Inhibitors of programmed cell death protein-1 (PD-1) and programmed cell death protein ligand-1 (PD-L1) are a group of checkpoint inhibitors being developed for the treatment of cancer. The United States Food and Drug Administration (FDA) has approved 6 different monoclonal antibodies targeting the PD-1/PD-L1 pathway: pembrolizumab (PD-1 inhibitor) (KEYTRUDA® prescribing information), nivolumab (PD-1 inhibitor) (OPDIVO® prescribing information), atezolizumab (PD-L1 inhibitor) (TECENTRIQ® prescribing information), durvalumab (PD-L1 inhibitor) (IMFINZI™ prescribing information), avelumab (PD-L1 inhibitor) (BAVENCIO® prescribing information), and cemiplimab-rwlc (PD-1 inhibitor) (LIBTAYO® prescribing information).

In the first-line setting, KEYNOTE-042 (Lopes et al 2018) demonstrated that single-agent pembrolizumab significantly improved overall survival (OS) compared with platinum-based chemotherapy in patients with advanced NSCLC, with ≥ 1% PD-L1 expression, but without *EGFR* mutation or *ALK* rearrangement. Treatment-related adverse events of Grade 3 or higher occurred in 113 (18%) of 636 patients treated in the pembrolizumab group and in 252 (41%) of 615 patients treated in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively (Mok et al 2019). Based on these results, the FDA approved pembrolizumab as a single agent for the first-line treatment of patients with Stage III NSCLC not amenable to surgical resection or definitive chemoradiation or metastatic NSCLC whose tumors express PD-L1 (tumor proportion score ≥ 1%) with no *EGFR* or *ALK* genomic tumor aberrations (KEYTRUDA® prescribing information).

Furthermore, pembrolizumab in combination with chemotherapy was also approved by the FDA in 2018, for patients with metastatic nonsquamous or squamous NSCLC.

In the KEYNOTE-189 study of patients with metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations, the addition of pembrolizumab to chemotherapy resulted in significantly longer OS (estimated rate of OS at 12 months was 69.2% versus 49.4%, hazard

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ratio of 0.49), longer progression-free survival (PFS) (median 8.8 months versus 4.9 months, hazard ratio of 0.52), and a higher response rate (47.6% versus 18.9%) than chemotherapy alone (Gandhi et al 2018).

In the KEYNOTE-407 study of patients with previously untreated metastatic squamous NSCLC, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer OS (median 15.9 months versus 11.3 months, hazard ratio of 0.64), longer PFS (median 6.4 months versus 4.8 months, hazard ratio of 0.56), and a higher response rate (57.9% versus 38.4%) than chemotherapy alone, regardless of the level of PD-L1 expression (Paz Ares et al 2018).

RATIONALE-307 (NCT03594747, known as BGB-A317-307) is a Phase 3, randomized, open-label, multicenter study investigating tislelizumab combined with either paclitaxel and carboplatin (Arm A) or nab-paclitaxel and carboplatin (Arm B) compared with paclitaxel and carboplatin alone (Arm C) in patients with untreated Stage IIIB or Stage IV squamous NSCLC from mainland China (Wang et al 2020). An assessment by an independent review committee (IRC) showed that PFS was significantly longer in both Arm A and Arm B (7.6 months), than in Arm C (5.5 months). The benefits were seen regardless of the level of PD-L1 expression. Response rates were better with tislelizumab, reaching 73% in Arm A and 75% in Arm B, compared with 50% in Arm C, as was the duration of response (DOR), which nearly doubled in Arm A (8.2 months) and Arm B (8.6 months), compared with that in Arm C (4.2 months).

RATIONALE-304 (NCT 03663205, known as BGB-A317-304) is a Phase 3, randomized, open-label, multicenter study conducted in mainland China, investigating tislelizumab in combination with platinum (carboplatin or cisplatin) and pemetrexed (Arm A) compared with platinum and pemetrexed alone (Arm B) in patients with histologically confirmed stage IIIB or IV nonsquamous NSCLC (Lu et al 2021). Addition of tislelizumab to chemotherapy led to significantly longer IRC-assessed PFS compared with chemotherapy alone (HR = 0.645 [95% CI: 0.462 to 0.902], p = 0.0044); the median PFS by IRC assessment was 9.7 months (95% CI: 7.7 to 11.5 months) and 7.6 months (95% CI: 5.6 to 8.0 months) in Arm A and Arm B, respectively. A higher ORR assessed by the IRC was observed with tislelizumab plus chemotherapy (57.4%; 95% CI: 50.6% to 64.0%) compared with chemotherapy alone (36.9%; 95% CI: 28.0% to 46.6%). The median DOR assessed by the IRC was longer in Arm A than that in Arm B, at 8.5 months (95% CI: 6.80 to 10.58 months) versus 6.0 months (95% CI: 4.99 months to not estimable), respectively. Higher ORR was observed across all TC PD-L1 expression cutoff subgroups in Arm A than in Arm B.

The addition of pembrolizumab or tislelizumab did not appear to increase the frequency of adverse events (AEs) that are commonly associated with chemotherapy regimens involving pemetrexed and platinum-based drugs. AEs of Grade 3 or higher in the pembrolizumab-combination group versus the placebo-combination group occurred in 67.2% versus 65.8% of the patients, respectively, in the KEYNOTE-189 study and in 69.8% versus 68.2% of the patients, respectively, in the KEYNOTE-407 study. In the RATIONALE-307 study, AEs leading to discontinuation of any treatment were reported in 12.5%, 29.7%, and 15.4% of patients in Arms A, B, and C, respectively. The most commonly reported ≥ Grade 3 AEs were hematologic in nature (eg, neutropenia) and were consistent with known chemotherapy-related AEs. Serious treatment-related AEs (TRAEs) were reported in 72 patients (37.5% [Arm A]; 38.9% [Arm B]; 23.6% [Arm C]); TRAEs leading to death were reported in

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6 patients (n = 1 [Arm A]; n = 2 [Arm B]; n = 3 [Arm C]), none of which were solely attributed to tislelizumab.

Three studies evaluated the efficacy and safety of atezolizumab in combination with chemotherapy (IMpower130 [Cappuzzo et al 2018], IMpower131 [Jotte et al 2018], and IMpower132 [Papadimitrakopoulou et al 2018]) as first-line treatment for advanced NSCLC. The use of the PD-L1 inhibitor atezolizumab in combination with chemotherapy demonstrated improved PFS in patients with Stage IV nonsquamous or squamous NSCLC.

The addition of atezolizumab to bevacizumab in combination with chemotherapy significantly improved PFS and OS among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and *EGFR* or *ALK* genetic alteration status (Socinski et al 2018; Reck et al 2019). TRAEs of ≥ Grade 3 occurred in 58.5% and 50.0% of patients in the atezolizumab/bevacizumab/chemotherapy group versus the bevacizumab/chemotherapy group, respectively.

CHECKMATE-227 included patients with recurrent or Stage IV NSCLC without previous treatment. Patients with a PD-L1 expression level of 1% or more were randomized in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab alone, or chemotherapy. The chemotherapy used was cisplatin or carboplatin, combined with either gemcitabine for patient with squamous cell NSCLC or pemetrexed for patients with nonsquamous disease. The median duration of OS was 17.1 months (95% confidence interval [CI], 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (p = 0.007), with 2-year OS rate of 40.0% and 32.8%, respectively. The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy (Hellmann et al 2019). CHECKMATE-9LA study randomized patients with Stage IV or recurrent NSCLC, to nivolumab + ipilimumab + 2 cycles of chemotherapy or 4 cycles of chemotherapy alone. Immunotherapy plus chemotherapy led to a significantly longer median OS than chemotherapy alone at the preplanned interim analysis (hazard ratio [HR] = 0.69, 96.71% CI: 0.55 – 0.87; p = 0.0006) and after a longer follow-up (a minimum of 12.7 months), a median OS of 15.6 months versus 10.9 months (HR = 0.66) , regardless of the levels of PD-L1 expression. Statistically significant improvements in PFS and ORR were also seen (Martin et al 2020). Based on these results, the FDA approved the combination of nivolumab plus ipilimumab as the first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1(≥ 1%) and the combination of nivolumab with ipilimumab plus 2 cycles of platinum-doublet chemotherapy as the first-line treatment for patients with metastatic or recurrent NSCLC.

Two immune checkpoint inhibitors targeting PD-1, nivolumab and pembrolizumab, were approved in 2015 for second-line therapy in patients with metastatic NSCLC whose disease progressed on or after platinum-containing chemotherapy. Among these, nivolumab demonstrated a survival benefit versus docetaxel in advanced nonsquamous NSCLC, resulting in 27% lower risk of death at a minimum follow-up of 13.2 months (median OS of 12.2 versus 9.4 months; ORR of 19% versus 12%), and a better safety profile than standard-of-care chemotherapy (Grade 3 and Grade 4 AEs: 10% versus 54%) (Borghaei et al 2015). Nivolumab was also evaluated in a Phase 3 clinical study in patients with squamous NSCLC whose disease had progressed during or after 1 prior platinum-based doublet chemotherapy regimen. Median survival was 9.2 months for nivolumab compared with 6.0 months for docetaxel (a HR of 0.59, p < 0.001). The response rate was 20% with nivolumab versus 9% with docetaxel (p = 0.008).

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The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (a HR of 0.62, $p < 0.001$) (Brahmer et al 2015). In 2016, another checkpoint inhibitor targeting PD-L1, atezolizumab, was approved for the same indication.

Despite this stream of new life-extending treatments involving anti-PD-(L)1 therapy, advanced or metastatic NSCLC remains an incurable disease for most patients. The interactions between the human immune system and tumor cells are continuous, dynamic, and evolving. Acquired resistance is described as the lack of response to immunotherapy after the patient initially responds to anti-PD-(L)1 then relapses or progresses (Sharma et al 2017). The frequencies of primary resistance in advanced NSCLC patients whose best responses were progressive disease in first-line immune checkpoint inhibitors with or without chemotherapy varied from 7% to 27%; whilst in a pretreated setting with immune checkpoint monotherapy, the reported rates ranged from 20% to 44% (Walsh and Soo 2020). For patients who experienced complete response, partial response, or stable disease from immunotherapy but tumor eventually relapsed or progressed, more effective treatment options with combating resistance and expanding the duration of response are needed.

1.2. Current Treatment of Non-Small Cell Lung Cancer and Unmet Clinical Needs

Docetaxel, pemetrexed, and erlotinib were 3 single agents approved by the US FDA and the European Medicines Agency (EMA) for use in the second- and subsequent-line setting for NSCLC after the first-line treatment of platinum-based doublet chemotherapy. In the US, erlotinib is limited to patients whose tumors have EGFR sensitizing mutation.

Docetaxel was the first agent demonstrating a survival benefit, compared with best supportive care (BSC) in patients with NSCLC that relapsed following first-line therapy, and was associated with an ORR in the range of 6% to 11% (Taxotere EPAR 2020).

Pemetrexed appeared to be noninferior to docetaxel in terms of efficacy outcomes in the second-line treatment of patients with advanced NSCLC (all histologies), with a median OS (mOS) of 8.3 months compared with an mOS of 7.9 months in the docetaxel arm (Hanna et al 2004); subsequent subgroup analysis revealed improved survival in patients with nonsquamous histologies, thus limiting its approval to patients with nonsquamous NSCLC (Alimta EPAR 2020).

Improved OS (median OS of 6.7 versus 4.7 months) was observed with erlotinib when compared with BSC in a randomized study that included patients with poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores (Tarceva EPAR 2020). Erlotinib has therefore often been used for patients who cannot receive cytotoxic chemotherapy due to poor ECOG PS.

Overall, the therapeutic index of these second-line NSCLC therapies has been restricted both by limited survival benefit and significant toxicities such as myelosuppression and neuropathy (docetaxel), diarrhea (pemetrexed, erlotinib), and rash (erlotinib) (Stinchcombe and Socinski 2008). Outcomes are poor for patients with previously treated, advanced or metastatic NSCLC; systemic chemotherapy (eg, docetaxel) or erlotinib provide only modest benefit (Al-Farsi and Ellis 2014; Stinchcombe and Socinski 2008).

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1.3. Antibody Therapy for Non-Small Cell Lung Cancer

Tislelizumab binds with high affinity to PD-1. It was engineered to minimize binding of fragment crystallizable region receptors (FcR) on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy.

Tislelizumab is being developed, as monotherapy or in combination with other drugs, for patients with locally advanced or metastatic NSCLC, esophageal squamous cell carcinoma, and other types of cancers (eg, hepatocellular carcinoma, gastric cancer, Hodgkin lymphoma, urothelial bladder cancer, B-cell lymphoid malignancies, nasopharyngeal cancer, and extensive-stage small-cell lung cancer).

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In addition, tislelizumab has no effector functions mediated through Fc gamma receptors (Zhang et al 2018). Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models.

Please refer to the tislelizumab IB for additional details regarding nonclinical studies of tislelizumab.

1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys.

No apparent toxicity was noted in single dose or 13-week repeat-dose monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The No Observed Adverse Effect Level (NOAEL) of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study, BGB-A317-Sitravatinib-301.

Please refer to the tislelizumab IB for more detailed information on the toxicology of tislelizumab.

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1.4.3. Clinical Pharmacology

Tislelizumab exhibited dose-proportional increase in exposure over the entire dose range (0.5 to 10 mg/kg). The population pharmacokinetic (popPK) analysis was performed based on pooled data (PK, dosing information, demographics, and patient or disease characteristics) from 2596 patients across 12 clinical studies. The PK of tislelizumab was best characterized using a 3-compartmental model with linear clearance mechanism. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume of distribution (V_c), and peripheral volumes 2 and 3 (V_2 and V_3, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal half-life ($t_{½}$) was estimated to be approximately 23.8 days. The accumulation ratios were estimated to be 2.14 and 2.49 for area under the serum concentration-time curve at steady state (AUC_{ss}) and minimum concentration at steady-state ($C_{min,ss}$), respectively. Steady state is expected to be reached in approximately 12 weeks.

The popPK analyses demonstrated that race, baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase (LDH), estimated glomerular filtration rate (eGFR), Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, and sum of products of perpendicular diameters (SUMPPD) of classical Hodgkin lymphoma (cHL) did not have statistically significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin level, age, sex, immunogenicity, and tumor type were found to be statistically significant covariates on the PK of tislelizumab; however, the exposure changes by these covariates were relatively small compared to overall estimated PK exposures range, and hence are not considered clinically meaningful.

Tislelizumab exposure-efficacy relationships were also evaluated in a range of solid tumor indications. No consistent and clinically relevant E-R relationship was observed for either the efficacy endpoint of objective response rate (ORR) or the safety endpoints of imAEs, IRRs, AEs ≥ Grade 3, AEs leading to dose modification, and AEs leading to drug discontinuation based on tislelizumab-treated patients.

1.4.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2021, there are 9 completed studies and 33 ongoing studies with tislelizumab, with over 3498 patients treated with tislelizumab as monotherapy or in combination with other therapies. Of these, 15 studies have preliminary data available and are presented in the tislelizumab IB edition 9.0, dated 20 October 2021. These include 6 monotherapy studies, 2 chemotherapy combination therapy studies; and 7 targeted therapy combination studies.

Refer to the tislelizumab IB for more detailed information on tislelizumab safety and efficacy data when given as monotherapy or in combination with chemotherapy.

1.4.4.1. Safety Assessment of Monotherapy Studies

A pooled analysis of monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy.

A total of 2150 patients were treated in the monotherapy studies included in the pooled safety analysis. Within the 7 solid tumor monotherapy studies, 1992 patients were treated. Refer to the

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tislelizumab IB for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

1.4.4.1.1. Treatment-Emergent Adverse Events

For the solid tumor monotherapy studies, a TEAE is defined as an AE that began or worsened in severity from baseline (pretreatment) after the first dose of study drug and before starting a new anticancer therapy or ≤ 30 days after the last dose of study drug, whichever occurred first. TEAEs also include immune-mediated adverse events (imAEs) and treatment-related SAEs that began or worsened from baseline ≤ 90 days after the last dose of study drug, regardless of whether a new anticancer therapy was started.

Of the 1992 patients in the solid tumor group of monotherapy studies, 1922 (96.5%) experienced ≥ 1 TEAE and 1391 patients (69.8%) experienced ≥ 1 TEAE considered treatment related. TEAEs ≥ Grade 3 in severity were experienced by 847 of 1992 patients (42.5%), and 269 patients (13.5%) experienced a ≥ Grade 3 TEAE considered treatment related. Serious TEAEs were reported in 706 patients (35.4%) and 209 patients (10.5%) experienced ≥ 1 serious TEAE considered treatment related. A total of 141 patients (7.1%) experienced a TEAE leading to death. The most commonly occurring TEAEs were anaemia (502 of 1992 patients, 25.2%), AST increased (18.0%), ALT increased (16.7%), decreased appetite (16.5%), and cough (15.1%).

Treatment-Emergent Adverse Events by Severity

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 847 (42.5%) experienced ≥ 1 TEAE of ≥ Grade 3 severity. The most commonly occurring ≥ Grade 3 TEAEs were anaemia (87 of 1992 patients, 4.4%), pneumonia (4.3%), AST increased (2.3%), hyponatraemia (2.1%), gamma-glutamyltransferase increased (1.7%), and hypertension (1.7%).

1.4.4.1.2. Treatment-Emergent Serious Adverse Events

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 706 (35.4%) experienced ≥ 1 treatment-emergent SAE. The most commonly occurring SAEs were pneumonia (95 of 1992 patients, 4.8%), pneumonitis (1.7%), dysphagia (1.2%), pleural effusion (1.0%), and pyrexia (1.0%).

Tislelizumab-Related Treatment-emergent Serious Adverse Events

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 209 (10.5%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most commonly occurring treatment-related SAE was pneumonitis (31 of 1992 patients, 1.6%). All other events occurred in less than 1% of patients.

1.4.4.1.3. Immune-Mediated Adverse Events

Anti-PD-1 therapies are known to cause imAEs in some patients and therefore have been defined as AEs of special interest (AESIs) in tislelizumab clinical studies.

Immune-mediated AEs are consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate

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etiology that were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an imAE that spans a window of days to several months.

All imAEs presented here are assessed as related to study drug by the investigator and categorized by the BeiGene Safety/Pharmacovigilance team. Certain imAEs have multiple Medical Dictionary for Regulatory Activities (MedDRA) terms associated with the same category. Special categories have been created to group patients experiencing these events.

Of the 1912 patients in the adjudicated solid tumor group of pooled monotherapy studies, 286 (15.0%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs of any grade were hypothyroidism (115 of 1912 patients, 6.0%), pneumonitis (2.1%), immune-mediated lung disease (0.7%), rash (0.7%), alanine aminotransferase increased (0.6%), and hyperthyroidism (0.6%). The categories of imAEs experienced by ≥ 1% of patients were immune-mediated hypothyroidism (118 of 1912 patients, 6.2%), immune-mediated pneumonitis (3.7%), immune-mediated hepatitis (1.8%), and immune-mediated skin adverse reaction (1.3%).

Adjudicated Immune-Mediated Adverse Events by Severity

Of the 1912 patients in the adjudicated solid tumor group of pooled monotherapy studies, 73 (3.8%) experienced ≥ 1 imAE that was ≥ Grade 3 in severity. The most commonly occurring ≥ Grade 3 imAEs were pneumonitis (15 of 1912 patients, 0.8%), interstitial lung disease (0.4%), ALT increased (0.3%), AST increased (0.3%), and hepatitis (0.3%).

Immune-mediated AEs of hepatitis, pneumonitis, colitis, endocrinopathies, myocarditis, and serious skin adverse reactions have been identified as risks of tislelizumab. Refer to the tislelizumab IB for more detailed information.

1.4.4.1.4. Infusion-Related Reactions

Infusion-related reactions (IRRs), including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon. Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 58 (2.9%) experienced ≥ 1 IRR of any grade. The most commonly occurring IRRs were “infusion-related reaction” (28 of 1992 patients, 1.4%), pyrexia (0.9%), rash (0.3%), hypotension (0.2%), nausea (0.2%), and pruritus (0.2%).

Infusion-Related Reactions by Severity

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 5 (0.3%) experienced ≥ Grade 3 IRRs. The most common ≥ Grade 3 IRR was “infusion-related reaction” (2 of 1992 patients, 0.1%). All other ≥ Grade 3 IRRs occurred in single patients.

1.4.4.1.5. Fatal Adverse Events

Deaths

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 163 (8.2%) died ≤ 30 days after their last dose of tislelizumab. The causes of death for these patients were adverse events (54 of 1992 patients, 2.7%), disease under study (2.6%), disease progression (2.5%), and “other” (0.4%). A total of 1230 patients (61.7%) died > 30 days after their last dose of tislelizumab. The causes of death for these patients were disease under study

(664 of 1992 patients, 33.3%), disease progression (22.7%), "other" (4.5%), adverse events (1.1%), and "missing" (0.1%).

Treatment-Emergent Adverse Events Leading to Death

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 141 (7.1%) experienced ≥ 1 TEAE leading to death. The most commonly occurring TEAEs leading to death were "death" (16 of 1992 patients, 0.8%), pneumonia (0.7%), multiple organ dysfunction syndrome (0.6%), general physical health deterioration (0.5%), hepatic failure (0.5%), and respiratory failure (0.5%).

Tislelizumab-Related Treatment-Emergent Adverse Events Leading to Death

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 20 (1.0%) experienced ≥ 1 tislelizumab-related TEAE leading to death. The most commonly occurring tislelizumab-related TEAEs leading to death were pneumonia (3 of 1992 patients, 0.2%), "death" (0.1%), hepatic failure (0.1%), multiple organ dysfunction syndrome (0.1%), and pneumonitis (0.1%). All other events occurred in single patients.

1.4.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 3 studies in solid tumors, BGB-A317_Study_001, BGB-A317-102, and BGB-A317-303, which are summarized below.

1.4.4.2.1. Study BGB-A317_Study_001

Study BGB-A317 Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation (0.5 to 10 mg/kg) and a dose-finding component with 3 parts (2 and 5 mg/kg given either once every 2 or 3 weeks, and a fixed dose of 200 mg given once every 3 weeks) to establish the maximum tolerated dose (MTD), if any, a recommended Phase 2 dose (RP2D), and followed by a Phase 1b component to investigate efficacy in select tumor types at the RP2D to further evaluate safety and tolerability of tislelizumab. Indication-specific cohorts included esophageal cancer, gastric cancer, hepatocellular carcinoma, and NSCLC.

Responses were assessed by the investigator per RECIST v1.1 criteria.

Of the 451 patients treated with tislelizumab in the study across all disease cohorts (Safety Analysis Set), best overall responses of CR were reported in 6 patients (1.3%) and of PR in 54 patients (12.0%). The resulting overall clinical response rate (CR + PR) was 13.3%. Additionally, there were 141 patients (31.3%) with a best overall response of stable disease.

Of the 49 patients in the NSCLC cohort (Safety Analysis Set), 12.2% (95% CI: 4.63% to 24.77%) of patients had a best overall response of CR or PR (tislelizumab IB).

1.4.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a nonrandomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 included a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 evaluated the activity and safety of tislelizumab at its RP2D of 200 mg given once every 3 weeks in indication specific expansion cohorts.

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Responses were assessed by the investigator per the RECIST v1.1 criteria.

Of the 300 patients treated in Study BGB-A317-102, efficacy data were presented for 238 patients (79.3%) treated with ≥ 1 dose of tislelizumab in the study (Safety Analysis Set) (data cutoff date: 01 December 2018). Of the presented indications, ORR was ≥ 15% in nasopharyngeal carcinoma (43%), microsatellite instability-high/mismatch repair deficient solid tumors (19%), NSCLC (18%), gastric cancer (17%), HCC (17%), and melanoma (15%). The median duration of response was only mature for the nasopharyngeal carcinoma cohort, which had a duration of response of 8.3 months (range 3.9 months to not estimable) with a median follow-up of 4.8 months.

The tumor responses in the patients of the NSCLC cohort (56 patients) in BGB-A317-102 showed no CR in any patient (0%) and PR in 10 patients (18%). Additionally, there were 21 patients (38%) with a best overall response of stable disease. Twenty-one patients (38%) had a best overall response of PD in this cohort (tislelizumab IB).

1.4.4.2.3. Study BGB-A317-303

Study BGB-A317-303 (RATIONALE 303) is a Phase 3, open-label, multicenter, randomized study to evaluate the efficacy and safety of tislelizumab monotherapy compared with docetaxel as second- or third-line treatment for patients with locally advanced or metastatic NSCLC of squamous- or nonsquamous histology. A total of 805 patients were randomly assigned in a 2:1 ratio to receive tislelizumab 200 mg intravenously once every 3 weeks (535 patients) or docetaxel 75 mg/m^2 intravenously once every 3 weeks treatment (270 patients).

OS, as the primary endpoint, was compared between tislelizumab and docetaxel treatment arms, both in the Intent-to-Treat (ITT) Analysis Set and the PD-L1-Positive Analysis Set, where PD-L1 positive was defined as ≥ 25% of TC with PD-L1 membrane staining via the Ventana SP263 assay.

Results from the interim analysis (data cutoff date: 10 August 2020), showed statistically significant and clinically meaningful improvement in OS with tislelizumab treatment in the ITT Analysis Set. The median OS was 17.2 months (95% CI: 15.28 to 20.04 months) for patients who received tislelizumab and 11.9 months (95% CI: 10.18 to 13.93 months) for patients who received docetaxel; the hazard ratio was 0.64 (95% CI: 0.527 to 0.778), with a 1-sided log-rank $p < 0.0001$. The improvement in OS with tislelizumab treatment was more prominent in the PD-L1-Positive Analysis Set, with a median OS of 19.1 months (95% CI: 16.82 to 25.79 months) for tislelizumab and 11.9 months (95% CI: 8.90 to 14.03 months) for docetaxel treatment; the hazard ratio was 0.52 (95% CI: 0.384 to 0.713), with a 1-sided log-rank $p < 0.0001$.

Longer median PFS was also observed with tislelizumab treatment compared with docetaxel treatment in the ITT Analysis Set, 4.1 months (95% CI: 3.75 to 5.03 months) versus 2.6 months (95% CI: 2.17 to 3.78 months), respectively.

Tumor response in the ITT Analysis Set showed a higher ORR rate (21.9% versus 7.0%) and longer DOR with tislelizumab treatment: the median DOR was 13.5 months (95% CI: 5.58 to 21.78 months) with tislelizumab treatment and 6.2 months (95% CI: 2.10 to 7.16 months) with docetaxel. The DCR rate was 55.7% and 42.2% for tislelizumab and docetaxel treatment, respectively (Zhou et al 2021).

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1.5. Background Information on Sitravatinib

Receptor tyrosine kinases (RTKs) are essential components of signal transduction pathways that mediate cell-to-cell communication (Hubbard and Miller 2007). They are a subclass of cell-surface growth-factor receptors with an intrinsic, ligand-controlled tyrosine-kinase activity. These single-pass transmembrane receptors that bind polypeptide ligands (mainly growth factors) play key roles in processes such as cell growth, differentiation, metabolism, and motility. In cancer, constitutive and aberrant activations of components of those pathways result in increased proliferation, survival, and metastasis. Therefore, these signaling pathways became prime targets for cancer therapy.

Sitravatinib (BGB-9468) is an orally bioavailable RTK inhibitor with potential antineoplastic activity. It is a potent inhibitor of multiple RTKs, including AXL, MER, MET, KIT, FLT3, RET, VEGFR1, VEGFR2, VEGFR3, PDGFRα, DDR2, TRKA, and TRKB. Sitravatinib targets are genetically altered in a variety of cancers and act as oncogenic drivers, promoting cancer development and progression. In addition to targeting genetically altered oncogenic drivers, sitravatinib targets are expressed in a number of immune cell types and promote an immunosuppressive tumor microenvironment (TME), thus providing a rationale for combining with PD-1 checkpoint inhibitor therapy. Along with the immunostimulatory effects, the immunomodulatory effects of sitravatinib mediated through VEGFR and KIT inhibition may further condition the TME in favor of antitumor activity. Preclinical data for sitravatinib indicate that it can increase PD-L1 expression in tumor cells, in vitro and in vivo. Pilot studies in syngeneic mouse tumor models also suggest that sitravatinib increases the proliferation and fraction of systemic/spleen CD4+ and CD8+ T lymphocytes and reduces the number of systemic myeloid-derived suppressor cells (MDSCs).

1.5.1. Pharmacology

Sitravatinib was demonstrated to be a potent inhibitor of the catalytic activity of a subset of closely related recombinant human RTKs with IC_{50} values ranging from 0.5 to 76 nmol/L. Sitravatinib showed potent activity in RTK-target dependent cell-based assays with IC_{50} values ranging from < 10 to 181 nmol/L. Consistent with this antitumor and antiangiogenic mechanism of action, sitravatinib demonstrated antitumor efficacy over a broad spectrum of human tumor xenograft models. In addition, concurrent treatment with sitravatinib greatly enhanced the activity of anti-PD-1 therapy in the CT26 syngeneic mouse tumor model.

In vitro, sitravatinib is a substrate of P-glycoprotein (P-gp) but is not a substrate of Breast Cancer Resistance Protein (BCRP), Organic Anion Transporter (OAT) 1 or 3, Organic Cation Transporter (OCT) 2, Organic Transporting Polypeptide (OATP) 1B1 or 1B3, or Multi-Antimicrobial Extrusion Protein (MATE) 1 or 2K. Sitravatinib inhibited the efflux transporters P-gp and BCRP, and Bile Salt Export Pump (BSEP) mediated transport with IC_{50} values of 0.838 μM, 1.51 μM, and 5.06 μM, respectively. Sitravatinib demonstrated direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, with IC_{50} values of 2.9 μM, 11 μM, 10 μM, 1.9 μM, 11 μM, and 0.81 μM, respectively.

Sitravatinib was more extensively metabolized in dogs than in mice, rats, and humans in vitro. In vitro results from the hERG assay demonstrate an IC_{50} of 0.6 μM (0.38 μg/mL) on the potassium current, which is approximately 227-fold higher than the mean free C_{max} at stead-state

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(0.00265 μM) in patients, suggesting a low risk for QTc prolongation. At the dose of 150 mg, the mean steady state plasma concentrations (adjusted for free fraction) observed in patients are approximately 290-fold lower than the hERG IC_{50} concentration. In vivo results demonstrated that there were no adverse effects on the cardiovascular system in telemetered dogs, including no effect on the QTc interval, when sitravatinib was administered as a single-dose to dogs at doses up to 4 mg/kg (mean 6-hour concentration of 0.072 μg/mL). Minor increases in vascular pressures were observed during the dog cardiovascular study.

Assessment of the neurological functional observation battery and respiratory evaluations (tidal volume, respiration rate, and minute volume) did not reveal any sitravatinib-related effects at doses up to 25 mg/kg in rats (Day 1 mean C_{max} = 4.9 μg/mL).

Please refer to the sitravatinib IB for additional details regarding nonclinical studies of sitravatinib.

1.5.2. Toxicology

In the 4-week repeated-dose toxicology study in Beagle dogs, sitravatinib was tolerated at doses up to 3 mg/kg/day, the highest dose tested (TX-MGCD516-006). No unscheduled deaths occurred in the study; however, 1 dog in the 3 mg/kg/day group was taken off dosing on Day 8 due to decreased body weight, emesis, loose feces, and dehydration. The remaining dogs in this dose group also exhibited decreased body weight and food consumption throughout the remainder of the dosing period. Upon necropsy, there were no treatment-related gross findings, clinical pathology changes, or microscopic findings attributed to sitravatinib at any dose level. Given the marked loss of body weight and decreased food consumption at 3 mg/kg/day, the NOAEL was considered 1 mg/kg/day.

In the 13-week repeat-dose study in dogs (TX-MGCD516-014), sitravatinib was tolerated at doses up to 2 mg/kg/day, the highest dose tested. There were no test article-related unscheduled deaths and no adverse sitravatinib-related ophthalmic or clinical pathology parameter changes. Target organ effects were limited to necrotizing vascular/perivascular inflammation in the serosa of the oviduct and uterus of 2 mg/kg/day group females. These reproductive organ effects in females were not present after the 4-week recovery period, demonstrating complete reversal of these effects. Based on the adverse effects in the reproductive organs of female dogs given 2 mg/kg/day of sitravatinib, the NOAEL was considered to be 2 mg/kg/day in males and 0.6 mg/kg/day in females.

In rats, VEGF-related target organs were identified, including the adrenal gland, Brunner's glands in the duodenum, lymphoid tissues, ovary, kidney (increased basophilic tubules), liver, pancreas, and tongue, bone, and teeth. All effects, except those in the kidney, bile duct, and pancreas, either recovered or showed partial recovery. Daily oral administration of sitravatinib to Crl:CD (Sprague Dawley) rats at a dose level of 25 mg/kg/day was not tolerated and resulted in adverse clinical observations, changes in body weight and food consumption, mortality, and early termination. Based on the severity of the sitravatinib-related toxicity at 25 mg/kg/day and mortality (though reduced) in animals given ≥ 10 mg/kg/day, the NOAEL was determined as 2.5 mg/kg/day.

Administration of sitravatinib in the 4-week repeat-dose rat study (TX-MGCD516-007) led to early deaths at 10 and 25 mg/kg/day. The cause of death and morbidity at these dose levels

consisted of adrenal hemorrhage and necrosis. Based on the severity of the sitravatinib-related toxicity at ≥10 mg/kg/day, the NOAEL is 2.5 mg/kg/day.

Sitravatinib was evaluated in a standard battery of Good Laboratory Practice genotoxicity studies (Ames, chromosome aberrations and in vivo rat micronucleus assays) and was considered negative for mutagenicity and clastogenicity.

Refer to the sitravatinib IB for more detailed information on the toxicology of sitravatinib.

1.5.3. Clinical Pharmacology

The PK profile of single-agent treatment with the sitravatinib freebase capsule has been evaluated in Studies 516-001 and MRTX-500 after single- and repeated-dose administration in patients with advanced solid tumor malignancies, and in Study 516-006 in healthy volunteers. Exposure parameters (maximum concentration [C_{max}] and area under the concentration-time curve [AUC]) were approximately dose proportional with single doses from 10 mg to 200 mg. After a 120 mg sitravatinib freebase single-dose administration under fasting condition, sitravatinib reached peak concentration in a median time (t_{max}) of approximately 6 to 8 hours. The arithmetic mean elimination half-life in patients is approximately 35.5 hours. After multiple oral administration, steady-state appeared to have been reached within 8 days and sitravatinib accumulated approximately 1.75- and 2-fold for C_{max} and AUC_{0-24} to that of a single dose, respectively. The food effect on sitravatinib PK is being evaluated.

Sitravatinib underwent multiple biotransformation reactions following single oral administration to healthy male volunteers, with metabolism mediated via oxidation, and oxidative O- and N-dealkylation, as well as secondary sulfation, demethylation, dehydrogenation, deamination, and reduction. Sitravatinib was the most abundant circulating component in human plasma, accounting for > 56% of the total drug-related exposure. M10 was the only major metabolite, accounting for approximately 19% of the total drug-related exposure. M10 was evaluated in nonclinical studies, and the data suggested M10 was pharmacologically active against sitravatinib RTK targets.

Following a single oral dose of radio-labelled sitravatinib, the majority of the administered radioactivity (98.9%) was recovered from feces, indicating fecal excretion as the major route of elimination for sitravatinib. Only 0.05% of the administered dose was excreted in urine as unchanged sitravatinib, indicating negligible renal clearance for sitravatinib.

Sitravatinib exhibits a pH-dependent solubility. The effect of acid-reducing agents on the PK of a single oral dose of sitravatinib in healthy adult subjects is being evaluated in Study 516-011. The emerging PK results showed that repeated oral doses of pantoprazole, a proton pump inhibitor (PPI), 40 mg once daily had no effect on the PK of sitravatinib. Given a PPI has no effect on the PK of sitravatinib, other acid-reducing agents (ie, H2 blockers, antacid) are also not expected to have any effect on the PK of sitravatinib.

Pharmacodynamic (PD) effects of sitravatinib treatment were examined by analyzing biomarkers VEGFA, soluble VEGF-R2 and soluble MET ectodomain (sMET) levels in patients' plasma samples collected before and/or after sitravatinib administration (at PK lead-in, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 Day 1) in Study 516-001. The EC_{50} for VEGF-R2 was determined to be 36.8 ng/mL which is similar to the IC_{50} (30.9 ng/mL) determined from a nonclinical tumor growth inhibition (TGI) model (Source:

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PK-MGCD516-011). At the clinical dose of 120 mg sitravatinib freebase QD, a geometric mean C_{trough} of 70.6 ng/mL was observed, which is almost 2-fold higher than the EC_{50}. The clinical dose of 120 mg sitravatinib freebase QD is expected to achieve an approximately near maximal effect on the drug target for sitravatinib.

Refer to the sitravatinib IB for more detailed information on clinical pharmacology of sitravatinib.

1.5.4. Clinical Experience With Sitravatinib

Sitravatinib monotherapy and sitravatinib in combination with nivolumab are being evaluated in ongoing studies. Refer to the sitravatinib IB for more detailed information on sitravatinib and the currently ongoing studies.

1.5.4.1. Safety Assessment of Monotherapy Study

Study 516-001 is a multicenter Phase 1/1b first-in-human clinical study evaluating the safety, PK, metabolism, pharmacodynamics (PD), and clinical activity of single-agent sitravatinib in patients with advanced solid tumor malignancies. The study determined that the 200-mg dose exceeded the MTD and 150 mg QD was initially considered the viable Phase 1b starting dose, which was subsequently decreased to 120 mg QD based on ongoing assessment of tolerability. The Phase 1b expansion included patients having tumors with selected histological diagnoses (renal cell carcinoma, castrate-resistant prostate cancer) or with histological diagnosis and/or tumor molecular markers (genetic alterations in sitravatinib RTK targets, or loss of function mutations in CBL, the negative regulators of AXL, MET, and PDGFR/KIT signaling). As of 26 June 2021, among the 193 patients with available safety data, 190 patients (98.4%) had experienced ≥ 1 AE regardless of causality, and 174 patients (90.2%) had experienced ≥ 1 treatment-related AE. Treatment-related AEs reported in ≥ 10% of patients are provided in Table 1.

Treatment-related Grade 3 to 5 AEs reported in ≥ 5% of patients were hypertension (21%), diarrhoea (10%), fatigue (7%), and palmar-plantar erythrodysaesthesia (PPE) syndrome (6%). Treatment-related Grade 4 AEs were reported in 3 patients and included lipase increased in 2 patients and febrile neutropenia in 1 patient. A treatment-related Grade 5 AE of cardiac arrest was reported in 1 patient.

Table 1: Summary of Treatment-Emergent, Treatment-Related Adverse Events (≥ 10%) by Preferred Term for Study 516-001

Adverse Event Preferred Term, n (%)	Patients (N = 193)
Any Related AE	174 (90.2)
Diarrhoea	99 (51.3)
Fatigue	83 (43.0)
Hypertension	78 (40.4)
Nausea	58 (30.1)
Decreased appetite	51 (26.4)
Vomiting	46 (23.8)
Palmar-Plantar Erythrodysaesthesia Syndrome	39 (20.2)
Aspartate aminotransferase increased	36 (18.7)

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Adverse Event Preferred Term, n (%)	Patients (N = 193)
Alanine aminotransferase increased	35 (18.1)
Hypothyroidism	33 (17.1)
Stomatitis	28 (14.5)
Weight decreased	28 (14.5)
Dysphonia	27 (14.0)
Abdominal pain	22 (11.4)
Constipation	22 (11.4)
Proteinuria	22 (11.4)
Dry mouth	21 (10.9)
Rash	21 (10.9)
Dizziness	20 (10.4)

Abbreviation: AE, adverse event.

Serious Adverse Events: Overall, 79 patients (40.9%) have experienced ≥ 1 SAE regardless of causality, and treatment-related SAEs were reported in 30 patients (15.5%). Treatment-related SAEs reported in 2 or more patients (≥ 1%) included diarrhoea in 6 patients (3.1%), nausea and vomiting in 5 patients each (2.6%), fatigue in 4 patients (2.1%), hypertension in 3 patients (1.6%), and headache, left ventricular dysfunction, pancreatitis, and pulmonary embolism in 2 patients each (1.0%).

Treatment Discontinuation and Deaths: Of the 193 treated patients, 191 (99.0%) have discontinued receiving study treatment, in most cases due to objective disease progression (92 patients [47.7%]), AE (31 [16.1%]), or subject withdrawal (31 [16.1%]). A total of 120 patients (62.2%) have discontinued the study due to death, with the most common cause of death being the primary disease under study.

1.5.4.2. Safety Assessment of Combination Study

Study MRTX-500 is an open-label, parallel group Phase 2 evaluation of sitravatinib in the combination with nivolumab in patients with locally advanced, unresectable or metastatic nonsquamous NSCLC. Patients who have experienced PD on or after treatment with a checkpoint inhibitor (CIT-experienced) as well as those who have experienced PD after treatment with platinum-based doublet chemotherapy (CIT-naïve) are enrolled. The sitravatinib treatment arm began with a lead-in evaluation of sitravatinib 120 mg once daily in combination with nivolumab administered by intravenous infusion, 240 mg once every 2 weeks or 480 mg once every 4 weeks. No protocol-defined dose-limiting toxicities (DLTs) were reported in the first 6 evaluable patients treated with the sitravatinib freebase at the starting dose of 120 mg once daily in combination with nivolumab. Based on the preliminary long-term tolerability assessments from Study 516-001 (Mirati 2018) and data from Study MRTX-500, Mirati decided to evaluate only the 120-mg dose of sitravatinib as this dose level should be adequate to achieve plasma exposure required for the inhibition of VEGF and TAM receptors necessary to achieve antitumor efficacy in the combination setting. The 120-mg dose level was selected as the RP2D. Based on the experience of patients enrolled into this study and in Study 516-001, 120 mg once daily was selected as the Phase 2 dose of sitravatinib in combination with nivolumab at 240 mg once every 2 weeks or 480 mg once every 4 weeks.

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As of 26 June 2021, patient data were entered in the clinical study database for 207 patients (median age: 66 years; range: 30 to 89 years) with advanced or metastatic NSCLC. A total of 156 patients were treated in the main study, 47 patients in the PK formulation substudy, and 3 patients in the PK food effect substudy. Enrollment is complete.

As of 26 June 2021, among the 206 patients with available safety data, 204 patients (99%) had experienced ≤1 AE regardless of causality; 193 patients (94%) had experienced treatment-related AEs; 191 patients (93%) had experienced sitravatinib-related AEs; and 149 patients (72%) had experienced nivolumab-related AEs. Treatment-related AEs reported in ≥ 10% of patients are provided in Table 2.

Treatment-related Grade ≥ 3 AEs were reported for 115 patients (56%) and included hypertension (15%), diarrhoea (12%), and weight decreased (5%) as the most common events. Sitravatinib-related Grade 3 AEs were reported for 97 patients (47%), and the most common events (in > 5% of patients) by PT were hypertension (15%), diarrhoea (11%), and weight decreased (5%). Nivolumab-related Grade 3 AEs were reported for 45 patients (23%), and no events occurred in > 5% of patients by PT.

Treatment-related Grade 4 AEs were reported for 8 patients (4%) overall, including 8 patients (4%) with sitravatinib-related Grade 4 AEs and 5 (2%) with nivolumab-related Grade 4 AEs. Grade 4 AEs related to sitravatinib only included acute kidney injury, cardiac failure, gastric ulcer perforation, hypertensive crisis, hyperuricemia, and lactobacillus test positive (in 1 patient each). Grade 4 AEs related to both sitravatinib and nivolumab included hemorrhagic shock, duodenal ulcer, lipase increased, lymphocyte count decreased, and pneumonitis (in 1 patient each), and Grade 4 AEs related to nivolumab only included cerebrovascular accident (1 patient). The Grade 4 events of hemorrhagic shock, duodenal ulcer, and lactobacillus test positive occurred in the same patient. Treatment-related Grade 5 AEs were reported for 2 patients (1%) overall and included cardiac arrest (related to sitravatinib) and cerebrovascular accident (related to sitravatinib) in 1 patient each.

Table 2: Summary of Treatment-Emergent, Treatment-Related Adverse Events (≥ 10%) by Preferred Term for Study MRTX-500

Adverse Event Preferred Term, n (%)	Patients (N = 206)		
	Sitravatinib Related	Nivolumab Related	Any Treatment Related
Any Treatment-Related AE	191 (92.7)	149 (72.3)	193 (93.7)
Diarrhoea	103 (50.0)	49 (23.8)	107 (51.9)
Fatigue	80 (38.8)	54 (26.2)	86 (41.7)
Nausea	80 (38.8)	29 (14.1)	80 (38.8)
Decreased appetite	68 (33.0)	21 (10.2)	68 (33.0)
Weight decreased	57 (27.7)	15 (7.3)	57 (27.7)
Hypertension	56 (27.2)	2 (1.0)	56 (27.2)
Vomiting	51 (24.8)	23 (11.2)	53 (25.7)
Hypothyroidism	20 (9.7)	42 (20.4)	46 (22.3)
Dysphonia	37 (18.0)	7 (3.4)	38 (18.4)
Palmar-plantar erythrodysaesthesia syndrome	35 (17.0)	2 (1.0)	35 (17.0)
Aspartate aminotransferase increased	31 (15.0)	23 (11.2)	34 (16.5)

Adverse Event Preferred Term, n (%)	Patients (N = 206)		
	Sitravatinib Related	Nivolumab Related	Any Treatment Related
Alanine aminotransferase increased	32 (15.5)	24 (11.7)	33 (16.0)
Stomatitis	27 (13.1)	6 (2.9)	29 (14.1)
Dysgeusia	24 (11.7)	4 (1.9)	24 (11.7)
Dry mouth	21 (10.2)	7 (3.4)	23 (11.2)
Proteinuria	21 (10.2)	5 (2.4)	22 (10.7)
Dehydration	20 (9.7)	8 (3.9)	21 (10.2)

Abbreviation: AE, adverse event.
Note: AEs are ordered by decreasing frequency within the overall "any treatment related" column.

Serious Adverse Events: Among the 206 patients receiving study treatment, 102 (50%) experienced ≥ 1 SAE regardless of causality. Treatment-related SAEs were reported in 51 patients (25%) overall, including sitravatinib-related SAEs in 42 patients (20%) and nivolumab-related SAEs in 24 patients (12%). Sitravatinib-related SAEs occurring in > 2 patients (> 1%) included diarrhoea (8 patients [4%]), pulmonary embolism (4 [2%]), deep vein thrombosis, nausea and vomiting (3 [1.5%] each). Nivolumab-related SAEs occurring in > 2 patients (> 1%) included diarrhoea and pneumonitis (4 patients [1.9%] each), and vomiting (3 [1.5%]).

Treatment Discontinuation and Deaths: Of the 206 treated patients, 200 (97%) have discontinued sitravatinib, in most cases due to disease progression (47%), or AE (25%), and 200 patients (97%) have discontinued nivolumab, in most cases due to disease progression (49%), or AE (24%). A total of 141 patients have died, with the primary cause of death being the primary disease under study (118/141 patients). One death was attributed to study treatment toxicity (Grade 5 event of cerebrovascular accident [verbatim term: stroke] related to sitravatinib).

Study BGB-900-103 is an open-label, multicenter, nonrandomized, multicohort, Phase 1b study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of sitravatinib in combination with tislelizumab in patients with advanced solid tumors (NCT03666143). As of 26 June 2021, safety data were available for 216 patients with advanced solid tumors who were treated with sitravatinib in combination with tislelizumab in this study (sitravatinib IB).

Among the 216 patients who received study treatment, 215 patients (99.5%) experienced ≥ 1 AE regardless of causality. A total of 210 (97%) experienced treatment-related AEs overall, including 203 (94%) experiencing sitravatinib-related AEs and 164 (76%) experiencing tislelizumab-related AEs. Treatment-related AEs reported in ≥10% of patients overall are presented in Table 3.

Treatment-related ≥ Grade 3 AEs were reported in 105 patients (49%), and those reported in 5 or more patients (≥ 3%) were hypertension (35 patients [16%]), ALT increased (12 [6%]), diarrhea (8 [4%]), and PPE syndrome (7 [3%]).

Treatment-related Grade 4 events were reported for 6 patients (2.8%) and treatment-related Grade 5 events were reported for 4 patients (death [2 patients, 0.9%], and cardiac failure and ischaemic stroke [1 patient each, 0.5%]).

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Table 3: Summary of Treatment-Emergent, Treatment-Related AEs (≥ 10%) by Preferred Term for Study BGB-900-103

Adverse Event Preferred Term, n (%)	Patients (N = 216)		
	Sitravatinib Related	Tislelizumab Related	Any Treatment Related
Any Related AE	203 (94.0)	164 (75.9)	210 (97.2)
Diarrhoea	92 (42.6)	31 (14.4)	96 (44.4)
Alanine aminotransferase increased	81 (37.5)	63 (29.2)	93 (43.1)
Aspartate aminotransferase increased	81 (37.5)	64 (29.6)	90 (41.7)
Hypertension	75 (34.7)	7 (3.2)	76 (35.2)
Hypothyroidism	14 (6.5)	60 (27.8)	62 (28.7)
Palmar-plantar erythrodysaesthesia syndrome	62 (28.7)	4 (1.9)	62 (28.7)
Decreased appetite	54 (25.0)	14 (6.5)	55 (25.5)
Nausea	52 (24.1)	14 (6.5)	54 (25.0)
Vomiting	40 (18.5)	5 (2.3)	41 (19.0)
Weight decreased	39 (18.1)	9 (4.2)	39 (18.1)
Blood creatine phosphokinase increased	19 (8.8)	28 (13.0)	35 (16.2)
Fatigue	32 (14.8)	12 (5.6)	35 (16.2)
Proteinuria	35 (16.2)	6 (2.8)	35 (16.2)
Rash	24 (11.1)	21 (9.7)	34 (15.7)
Dysphonia	27 (12.5)	4 (1.9)	29 (13.4)
Blood creatine phosphokinase MB increased	22 (10.2)	14 (6.5)	25 (11.6)
Blood lactate dehydrogenase increased	21 (9.7)	17 (7.9)	25 (11.6)
Blood bilirubin increased	24 (11.1)	11 (5.1)	24 (11.1)
Stomatitis	23 (10.6)	1 (0.5)	24 (11.1)
Platelet count decreased	19 (8.8)	17 (7.9)	22 (10.2)

Abbreviation: AE, adverse event.
Note: AEs are ordered by decreasing frequency within the overall "any treatment related" column.

Serious Adverse Events: Among the 216 patients with available safety data, 118 patients (55%) experienced at least one SAE regardless of causality. Treatment-related SAEs were reported in 70 patients (32%), and included diarrhea in 8 patients (4%), hepatic function abnormal in 5 patients (2%), and pneumonia and transaminases increased in 4 patients each (2%). All other treatment-related SAEs occurred in 2 or fewer patients (<1 %) overall.

Treatment Discontinuation and Deaths: Of the 216 patients receiving study treatment, 179 patients (83%) have discontinued sitravatinib and 176 (82%) have discontinued tislelizumab treatment. The most common reasons for discontinuation from sitravatinib were progressive disease (116 patients [54%]), AE (42 [19%]), and withdrawal by patient (15 [7%]). The most common reasons for discontinuation from tislelizumab were progressive disease (128 patients [59%]), AE (26 [12%]), and withdrawal by patient (18 [8%]). A total of 103 deaths have been reported, and the primary cause of death was progressive disease (83 of 103 patients [81%]).

1.5.4.3. Efficacy Assessment of Sitravatinib Monotherapy

Efficacy results are available from the Phase 1b study 516-001(Werner et al 2017). In this Phase 1b dose expansion study, sitravatinib was evaluated in different patient populations:

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- Tumors harboring genetic alterations resulting in dysregulation of sitravatinib's RTK targets:
  - NSCLC with activating genetic alteration in *RET*, *KDR*, *PDGFRA*, *KIT*, *NTRK*, *DDR2*, *MET*, *AXL* or with loss of function mutation with *CBL*
  - Any solid tumor malignancy with genetic alteration of sitravatinib RTK targets or *CBL*
- Metastatic renal cell carcinoma (mRCC) refractory to VEGF pathway inhibitors (simultaneously targeting MET and VEGFR)
- Castration resistant prostate cancer (CRPC) with bone metastases

As of 18 April 2018, 29 patients were enrolled in the Phase 1b mRCC study, after failure of prior anti-angiogenic therapy. Sitravatinib monotherapy showed 20% confirmed ORR among 20 evaluable patients. Prolonged stable disease for ≤ 24 weeks was observed in 6 additional patients.

As of 4 September 2018, 16 patients were enrolled in the Phase1b CBL loss of function cohort. Among 8 clinical activity evaluable patients (received ≤ 1 cycle of sitravatinib for more than 80% of assigned total dose and ≤ 1 on-study disease assessment), sitravatinib monotherapy demonstrated anti-tumor activity in 2 patients (one with NSCLC and one with melanoma, respectively).

1.5.4.4. Efficacy Assessment of Sitravatinib Combination with PD-1 Blocking Agent

Early signs of clinical activity from the Phase 2 MRTX-500 study have been observed in patients with nonsquamous NSCLC, who have experienced disease progression following prior anti-PD-(L)1 therapy. As of the cutoff date of 01 June 2021, the median OS was 14.9 months (95% CI: 9.3 to 21.1 months) in patients with nonsquamous NSCLC who had clinical benefit from prior CPI therapy and received the sitravatinib plus nivolumab treatment in the study (N = 68) (Leal et al 2021). Among the 68 patients, the ORR was 18% (12 responders of 68 patients) including 2 CRs (3%) and 10 PRs (15%), with a median DOR of 12.8 months; the median PFS was 5.7 months (95% CI: 4.9 to 7.6 months) (Leal et al 2021). The combination of sitravatinib with nivolumab is a rational approach to restore or enhance the clinical activity of CIT in patients with immunotherapy resistant NSCLC.

Study 516-003 is a Phase 2 study of sitravatinib in combination with nivolumab in patients diagnosed with advanced or metastatic urothelial carcinoma. In a cohort of patients (N = 22, data cutoff date of 17 October 2019) who have progressed on or after CIT as the most recent treatment before the study, and were previously treated with platinum-based chemotherapy, confirmed ORR was 27% whilst 86% of patients had CR/PR/stable disease longer than 12 weeks (Msaouel et al 2019). In cohort of CIT naïve and platinum treated patients, sitravatinib plus nivolumab demonstrated consistent clinical activity (confirmed ORR 37%, clinical benefit rate 73%, median PFS 4.0 months, median DOR 5.6 months, and median OS 9.2 months) as of the data cutoff on 30 July 2020 (Msaouel et al 2020).

In Study BGB-900-103, Cohort A and Cohort F enrolled patients with nonsquamous and squamous metastatic NSCLC, respectively, with the disease refractory/resistant to anti-PD-(L)1 therapy. From December 2018 to June 2020, a total of 47 patients with NSCLC, nonsquamous

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(n = 24) and squamous (n = 23), were enrolled. As of the data cutoff date of 13 October 2020, the confirmed ORR was 13.6% and the DCR rate was 86.4%. The median DOR was 6.90 months (95% CI: 3.06 to not evaluable). The median PFS was 5.2 months (95% CI: 4.1 to 5.9 months). As of the data cutoff date, the median OS was 10.1 months (95% CI: 6.1 to 18.1 months), with a median follow-up duration of 12.4 months. The OS data were not mature (ESMO Poster 2021).

1.6. Study Rationales

1.6.1. Rationale for Tislelizumab in the Treatment of Non-Small Cell Lung Cancer

High levels of FcγR-expressing MDSCs (eg, M2 macrophage, MDSC) in tumor tissues predict a poor survival of tumor-bearing animals after anti-PD-1 monoclonal antibody treatment; this is possibly due to Fc-FcγR-mediated antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T cells (Gül et al 2015; Prieto et al 2015; Makarova-Rusher et al 2015; Beers et al 2016; Dahan et al 2015). As a no- to low-FcγR-binding agent (thus causing minimal ADCC/ADCP effect), tislelizumab may show improved efficacy and reduced toxicity in NSCLC.

Latest data collected from the Phase 1 BGB-A317_Study_001, tislelizumab monotherapy has established a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies. Finally, data from Study BGB-A317-303 showed superiority with tislelizumab monotherapy as compared with docetaxel for the treatment of patients with squamous- or nonsquamous NSCLC in the second- or third-line settings (Section 1.4.4.2.3).

1.6.2. Rationale for Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first-in-human Study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate and the fixed dosage of 200 mg once every 3 weeks was determined to be the clinical recommended dose for tislelizumab.

In the Study BGB-A317_Study_001, the dose of tislelizumab was escalated from 0.5 mg/kg to 10 mg/kg once every 2 weeks and no maximum tolerated dose was reached. For dose schedule and dose exploration, a dosage of 2 mg/kg or 5 mg/kg scheduled for either once every 2 weeks or once every 3 weeks and a fixed dose of 200 mg once every 3 weeks were evaluated. All dosages tested were tolerated. Comparable safety and efficacy profiles were observed between the 2 and 5 mg/kg dose levels with an administration frequency of either once every 2 weeks or once every 3 weeks, suggesting no clear dose-dependence across these regimens. Also, exposure-response analysis indicated a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of tumor types based on the combined data including dose ranges up to 10 mg/kg. The less frequent regimen of once every 3 weeks regimen was selected based on the similarity in efficacy and safety events observed between the once every 2 weeks and once every 3 weeks regimens tested in the study. Combined with the forementioned observations, the fixed dose of 200 mg once every 3 weeks was selected to be the recommended dose as tislelizumab concentrations with this dose largely overlapped with those observed with the 2 mg/kg and 5 mg/kg once every 3 weeks.

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The efficacy and safety of tislelizumab at the recommended dosage of 200 mg once every 3 weeks have been subsequently studied in multiple clinical studies across different tumor types, including NSCLC. With this dose regimen, marketing approvals have been granted in China for tislelizumab in combination with chemotherapy as the first-line treatment and for tislelizumab monotherapy as the second- or third-line treatment for patients with locally advanced or metastatic NSCLC. In this study, the dose regimen of 200 mg once every 3 weeks will be used for tislelizumab to evaluate its combination with sitravatinib in patients with NSCLC.

1.6.3. Rationale for Selection of Sitravatinib Dose

The 120 mg QD freebase dose level was selected as the optimized dose for clinical evaluation in the planned Phase 2 and Phase 3 studies based on the totality of evidence available for clinical activity, safety, and supportive pre-clinical and clinical pharmacology data including E-R analysis.

In Study 516-001, the safety, PK, and clinical activities of sitravatinib following oral administration of doses ranging from 10 mg to 200 mg were evaluated in patients with advanced solid tumor malignancies. Based on the Phase 1 dose escalation, 150 mg QD freebase formulation was established as the MTD and the starting dose for the Phase 1b components. During the conduct of the study, the dose was decreased from 150 mg QD to 120 mg QD because of early suggestion that treatment discontinuations may be higher than expected and that tolerability over a longer treatment period favors a lower dose (preliminary data from Study 516-001). As a result, 120 mg sitravatinib freebase was selected for further assessment in the Phase 2 Study MRTX-500.

Pharmacokinetic results demonstrated that sitravatinib exposure increased approximately dose proportionally when orally administered at doses between 10 and 200 mg sitravatinib freebase QD in patients. At the 120 mg QD dose level, between-patient variability was approximately 50% to 60%. The following preclinical and clinical pharmacology findings support 120 mg QD as the appropriate dose to achieve efficacy:

- Sitravatinib targets several receptor tyrosine kinases that have been shown in preclinical models to mediate an immunosuppressive TME. As determined in enzyme and cellular assays, the key target kinases it showed potency against include AXL, MERT, VEGFR2, KIT, and MET. The observed mean steady-state trough level with sitravatinib 120 mg QD in patients was 73.4 ng/mL (Study MRTX-500). The free fraction adjusted trough plasma concentration of sitravatinib (1.64 nM based on 98.6% plasma protein binding) compared with the biochemical and cellular IC_{50} values (ranging from 1.5 to 70 nM) for the key target kinases suggests several targets are only partially inhibited at the end of the dosing interval using the 120 QD dose level. Lower dose levels result in even lower predicted target kinase inhibition at the end of the dosing interval. These data suggest the 120 mg QD freebase dose is required to more fully inhibit key kinases for the entire dosing interval.
- PK/PD analysis using PK and biomarkers data from Study 516-001 showed a concentration- and dose-dependent modulation of s-VEGF-R2. The EC_{50} was determined to be 36.8 ng/mL. The clinical dose of 120 mg sitravatinib freebase QD achieved the mean $C_{trough,ss}$ (73.4 ng/mL; Study MRTX-500) approximately 2-fold higher

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than the EC_{50} and is expected to achieve an a near-maximal effect on the drug target for sitravatinib.

Exposure-response analyses were performed for efficacy endpoints (ie, clinical benefit [CB] and ORR) and safety endpoints (ie, fatigue, diarrhea, system blood pressure, PPE, any TEAEs ≥ Grade 3, and any AEs ≥ Grade 3 and 4) in patients with NSCLC receiving nivolumab and sitravatinib combination regimens. Overall, statistically significant E-R relationship was observed for CB, ORR, and PPE or oral dysaesthesia (ie, increasing the probabilities of ORR and CB, as well as AE PPE or oral dysaesthesia with increasing sitravatinib exposure). Sitravatinib steady-state exposure associated with 120 mg QD is predicted to achieve approximately 85.4% probability for CB, which is near the maximal effect and 22.2% probability for ORR. In contrast, doses lower than 120 mg QD (eg, 80 mg QD) is expected to be suboptimal for efficacy based on the predicted probability for CB and ORR of 80% and 13.6%, respectively. From the safety/tolerability perspective, sitravatinib 120 mg QD is predicted to have approximately 24% probability for the AE palmar-plantar incidence. Increasing sitravatinib exposure or doses might result in a higher probability of any grade PPE or oral dysaesthesia incidence.

Sitravatinib 150 mg QD freebase showed treatment discontinuations at a higher-than expected rate (Study 516-001) and is predicted to result in a higher probability for the AE PPE incidence based on E-R analysis. In contrast, sitravatinib freebase 80 mg QD is expected to be sub-optimal for efficacy based on pre-clinical and clinical pharmacology properties and E-R analysis. Thus, sitravatinib 120 mg QD freebase was the optimal dose selected for further clinical evaluation in combination regimens based on the totality of clinical data, preclinical and clinical pharmacology properties, and E-R results.

To introduce malate capsule formulation into the development of sitravatinib, Studies 516-006 and BGB-Sitravatinib-101 have been conducted to compare the systemic exposure of sitravatinib between the malate and the freebase capsule formulation. The results showed that the PK exposures of 100 mg malate capsule formulations and 120 mg freebase capsule formulations were comparable (sitravatinib IB). Therefore, the 100 mg QD dose of sitravatinib malate capsule is recommended for further evaluation in NSCLC patients.

1.6.4. Rationale for Dose Selection of Sitravatinib and Tislelizumab in Combination Treatment

Given the low potential of pharmacokinetic and pharmacodynamic drug-drug interaction between tislelizumab and sitravatinib, the dose regimens recommended for sitravatinib and tislelizumab monotherapy have been adopted for combination assessment and have been evaluated in patients with advanced or metastatic malignancies (including NSCLC) in Studies BGB-900-103 and BGB-900-104. As of June 2021, a total of 327 patients were enrolled and the tolerability data further supported the combination of tislelizumab 200 mg once every 3 weeks and sitravatinib freebase capsule formulation 120 mg QD (Section 1.5.4). The dose regimen of 200 mg tislelizumab once every 3 weeks in combination with 120 mg sitravatinib freebase capsule QD are tolerable. The PK exposures of a single dose of 100 mg sitravatinib malate capsule and 120 mg freebase capsule in healthy subjects are considered comparable (Section 1.6.3). Therefore, tislelizumab 200 mg once every 3 weeks in combination with sitravatinib 100 mg QD malate capsule will be used in this study.

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1.6.5. Rationale for Docetaxel as the Comparator

Docetaxel 75 mg/m² administered intravenously once every 3 weeks was chosen as the active control. This dosing regimen is recommended as the standard of care in the second- and third-line treatment setting for NSCLC based on international guidelines used consistently and globally, including within the European Union, the United States of America, and China, and it is also a commonly used standard treatment option in all regions participating in the studies.

Furthermore, despite the potential differences between Asian and Western patients with lung cancer in terms of epidemiology (eg, risk factors, demographics, and genetic susceptibility), the treatment outcome with docetaxel is similar between patients in China and Europe with advanced non-oncogene driven NSCLC. A median OS of 7 to 10 months was observed in the docetaxel arms across pivotal studies with other anti-PD-1/PD-L1 agents, including CHECKMATE 017, CHECKMATE057, KEYNOTE-010, and OAK studies (Brahmer et al 2015; Borghaei et al 2015; Herbst et al 2016; Rittmeyer et al 2017). Consistent median OS was reported for docetaxel in a Phase 3 study comparing docetaxel with pemetrexed as second-line treatment in Chinese patients with NSCLC (Sun et al 2013).

1.6.6. Rationale for Combination of Tislelizumab and Sitravatinib in the Treatment of Non-Small Cell Lung Cancer

Cancer cells face selective pressures while being treated, and mutations occurring in individual cancer cells represent continuous evolution of the original cancer. Almost all malignancies develop resistance to anticancer therapies eventually. This is also the case for treatment with checkpoint blockade agents where acquired resistance occurs in a large portion of treated patients who achieved an initial meaningful response. This phenomenon of acquired resistance helps cancer cells adapt to the environment and survive immune attacks and is a reminder of the therapeutic challenges that need to be overcome (Syn et al 2017). One of the mechanisms is an immunosuppressive TME. It includes a collection of various cell types that have switched sides and protect the cancer cells from immune system attacks. Various RTKs have been implicated in creating and maintaining an immunosuppressive TME.

Combining an immunotherapeutic PD-1 checkpoint inhibitor with an RTK inhibitor that has both immunomodulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone. By targeting the specific RTK receptors, an immunosuppressive TME is converted to an immune-supportive TME, which makes the cancers more likely to respond to checkpoint inhibitor treatment. The use of RTK blocking agents to treat cancer is well established based on robust clinical efficacy achieved with well tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected targeted therapies have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, thereby increasing the frequency and function of effector immune elements while decreasing the number and function of immune suppressor cells.

Sitravatinib is a potent, spectrum-selective RTK inhibitor. It inhibits several closely related RTKs, including members of the TAM family (TYRO3, AXL and MER), as well as VEGFR2 and KIT. This inhibition weakens the cancer's defenses in the TME. First, the antitumor activity of sitravatinib may promote the release of tumor antigens. Second, inhibition of the split kinase receptors VEGFR-2 and KIT may decrease the number of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thus promoting the expansion and migration of

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antitumor cytotoxic T cells and their infiltration into tumor tissue. Third, sitravatinib may reverse the immunosuppressive effects within the TME that are mediated by the TAM receptors through inhibition of MERTK, resulting in an increased number of M1 versus M2-polarized macrophages and release of interleukin (IL)-12, IL-6, and tumor necrosis factor. These downstream effects enhance CD8+ T cell activation, and through the inhibition of AXL, promote increased antigen presentation through termination of the Toll-like receptor-dependent inflammatory response in dendritic cells.

Treatment options after prior immunotherapy in lung cancer remain a significant unmet medical need. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy is a rational approach to improving outcomes in patients. Targeting RTKs has been shown to stimulate the immune system and cause synergistic effects that stimulate tumor shrinkage.

Early clinical studies demonstrated encouraging data that support this hypothesis. In a Phase 1b/2 study of lenvatinib (a multikinase inhibitor of vascular endothelial growth factor receptor [VEGFR] 1 to 3, fibroblast growth factor receptor 1 to 4, platelet-derived growth factor receptor α, RET and KIT) plus pembrolizumab in patients with histologically and/or cytologically confirmed metastatic NSCLC, the combination therapy showed promising clinical activity in NSCLC (Taylor et al 2020). With 52% of patients experienced anti-PD-(L)1 as prior therapy, the ORR at 24 weeks was 33.3% per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) in previously treated patients while the median DOR was 10.9 months and median PFS was 5.9 months.

Another Phase 2 study MRTX-500 demonstrated encouraging preliminary OS data with sitravatinib in combination with nivolumab in patients with NSCLC that progressed on or after checkpoint inhibitor. The median OS was 14.9 months for the subset of patients with prior clinical benefit who received the combination in the second- or third-line of treatment (Leal et al 2021). Study BGB-900-103 showed additional promising efficacy data with the combination treatment of sitravatinib and tislelizumab for patients with nonsquamous (Cohort A) or squamous (Cohort F) metastatic NSCLC that are refractory/resistant to anti-PD-(L)1 therapy (see details in Section 1.5.4.4). In both of these studies, anti-PD-(L)1 therapy was required to be the most recent prior treatment. As patients who have disease progression on or after the upfront anti-PD-(L)1 therapy that was followed by chemotherapy are also refractory/resistant to anti-PD-(L)1 therapy, based on the mechanism of sitravatinib, it is speculated that sitravatinib in combination with a checkpoint inhibitor is beneficial to those patients, just as to the subset of patients who received anti-PD-(L)1 therapy as the most recent prior treatment.

In summary, selective RTKs inhibit key molecular and cellular pathways strongly implicated in checkpoint inhibitor resistance and therefore represent reasonable strategies to enhance or restore antitumor immunity when combined with anti-PD-(L)1 monoclonal antibodies. Therefore, tislelizumab, which belongs to the same class of PD-1 blocking antibodies, may elicit comparable antitumor activity when combined with sitravatinib.

1.7. Benefit-Risk Assessment

Patients with locally advanced or metastatic NSCLC represent a population with a great unmet medical need. Docetaxel, pemetrexed, and erlotinib are currently the 3 approved systemic therapy available to patients with NCSLC worldwide with manageable safety profiles

(characterized by a relatively moderate incidence of dose reductions or drug discontinuations; see Section 1.2).

Immunotherapy with checkpoint inhibitors has demonstrated responses in patients with NSCLC. Combination therapy with a small-molecule inhibitor of the VEGFR pathway may improve the clinical efficacy of immunotherapies and overcome resistance to checkpoint inhibitor therapy. Access to new treatment options and/or treatment options after prior immunotherapy remains a significant unmet medical need. Based on the available data for tislelizumab and sitravatinib and publications for other PD-(L)1 inhibitors and other small-molecule inhibitors targeting the VEGFR pathway, the combination of sitravatinib and tislelizumab may elicit greater antitumor activity and have a manageable safety profile.

More than 1000 patients have been treated with sitravatinib either as monotherapy or in combination with other drugs. Nonclinical toxicology studies, as well as clinical safety data from the Phase 1/1b and Phase 2 studies, suggest that AEs associated with sitravatinib are similar to those observed with other small-molecule inhibitors of the VEGFR pathway. For further discussion on the safety profile of sitravatinib, please refer to the sitravatinib IB.

More than 3000 patients have been treated with tislelizumab as monotherapy at clinically relevant doses (≥ 2 mg/kg) or in combination with other drugs. The safety profile is consistent with known class effects of anti-PD-1 antibodies and includes mostly mild and moderate AEs. Very few Grade 3 or Grade 4 imAEs have been observed, which are generally reversible and manageable with study treatment interruption and/or steroid treatment. For further discussion on the safety profile of tislelizumab, please refer to the tislelizumab IB.

1.8. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To compare the overall survival (OS) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy
- To compare the progressive-free survival (PFS) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the Independent Review Committee (IRC)

2.1.2. Secondary Objectives

- To compare the PFS of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the investigator
- To compare the overall response rate (ORR), duration of response (DOR), and disease control rate (DCR) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy as assessed by the IRC
- To evaluate the safety and tolerability of tislelizumab and sitravatinib combination therapy compared with that of docetaxel monotherapy
- To evaluate and compare health-related quality of life (HRQoL) between the tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy via patient reported outcomes (PROs) using EORTC-QLQ-C30 (measuring general cancer) and its lung cancer module, QLQ-LC13, and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)
- To characterize the pharmacokinetics (PK) of sitravatinib when given in combination with tislelizumab, if data permit

2.1.3. Exploratory Objectives

- To compare the combination of tislelizumab with sitravatinib versus docetaxel monotherapy, as measured by ORR, DOR, and DCR assessed by the investigator
- To explore the predictive and prognostic effect of PD-L1 expression level
- To characterize the PK of the active metabolite M10 of sitravatinib when given in combination with tislelizumab, if deemed necessary
- To characterize the PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To explore potential biomarkers that may correlate with clinical responses or resistance to sitravatinib in combination with tislelizumab

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2.2. Study Endpoints

2.2.1. Primary Endpoint

- OS, defined as the time from randomization to death from any cause
- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRC based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause, whichever occurs first

2.2.2. Secondary Endpoints

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator based on RECIST v1.1, or death from any cause, whichever occurs first
- ORR, defined as the proportion of patients with PR or CR as determined by the IRC based on RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, as determined by the IRC based on RECIST v1.1, or death from any cause, whichever occurs first
- DCR, defined as the proportion of patients whose best overall response (BOR) is CR, PR or stable disease as determined by the IRC based on RECIST v1.1
- HRQoL, defined as changes in patient-reported outcomes (PROs), according to the European Organisation for Research and Treatment of Cancer (EORTC) core cancer (QLQ-C30) and its lung cancer module, QLQ-LC13, as well as the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) from time of randomization to End of Treatment Visit (EOT), death or study discontinuation whichever comes first.
- Incidence and severity of TEAEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0
- Plasma concentrations and the derived PK parameters of sitravatinib if data permit

2.2.3. Exploratory Endpoints

- ORR, defined as the proportion of patients with PR or CR as determined by the investigator based on RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, as determined by the investigator based on RECIST v1.1, or death from any cause, whichever occurs first
- DCR, defined as the proportion of patients whose BOR is CR, PR, or stable disease based on RECIST v1.1 by the investigator
- To explore the predictive and prognostic effect of PD-L1 expression level on OS
- To evaluate the predictive and prognostic effect of PD-L1 expression level using PFS, ORR, and DCR by the IRC and investigator

- Plasma concentrations and the derived PK parameters of M10 if data permit
- Serum concentrations of tislelizumab and the incidence of antidrug antibodies (ADAs)
- Potential biomarkers such as PD-L1 expression, gene expression profiling (GEP), tissue and blood tumor mutation burden (tTMB/bTMB) and microsatellite instability (MSI), and alterations in tissue and circulating tumor DNA (ctDNA), and the association of biomarkers with disease status, and response/resistance to sitravatinib in combination with tislelizumab

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3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, randomized, multicenter, Phase 3 clinical study evaluating the efficacy and safety of tislelizumab in combination with sitravatinib compared with docetaxel in patients with locally advanced or metastatic NSCLC who have disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy.

The study will be conducted at approximately 100 centers globally. The study will consist of a screening period, a treatment period, and a long-term follow-up period. Approximately 420 patients with locally advanced or metastatic NSCLC, who received no more than 2 lines of prior systemic therapy, will be enrolled and randomized in a 1:1 ratio to receive either tislelizumab in combination with sitravatinib, or docetaxel monotherapy.

Patients must have had radiographic progression per RECIST v1.1 on or after anti-PD-(L)1 containing therapy for locally advanced and unresectable or metastatic NSCLC. If anti-PD-(L)1-containing therapy is not the most recent systemic treatment, patients should also have radiographic progression per RECIST v1.1 on or after the most recent systemic treatment. Adjuvant or neo-adjuvant chemotherapy will be counted as 1 prior line of chemotherapy if the disease progressed on or within 6 months after the completion of the last dose. In locally advanced and unresectable NSCLC, disease progression on or within 6 months after the end of systemic therapy as part of prior curatively intended multimodal therapy will count as 1 prior line of systemic therapy. If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course counts as 1 line of therapy (patients who received anti-PD-[L]1 antibody as consolidation treatment following definitive chemoradiation for unresectable Stage III NSCLC can be enrolled immediately after disease progression, if the disease progression occurred within 6 months after the end of platinum-based chemotherapy component of the definitive chemoradiation). Maintenance therapy following platinum-based chemotherapy is not considered as a separate line of therapy. No other prior immunotherapies, including but not limited to anti-TIGIT, anti-OX40, and anti-CD137, will be allowed (prior anti-CTLA4 used in combination with anti-PD-[L]1 is permitted); no prior anticancer therapy having the same mechanism of action as sitravatinib (eg, tyrosine kinase inhibitor with a similar target profile or anti-VEGF or anti-VEGFR antibody) will be allowed either.

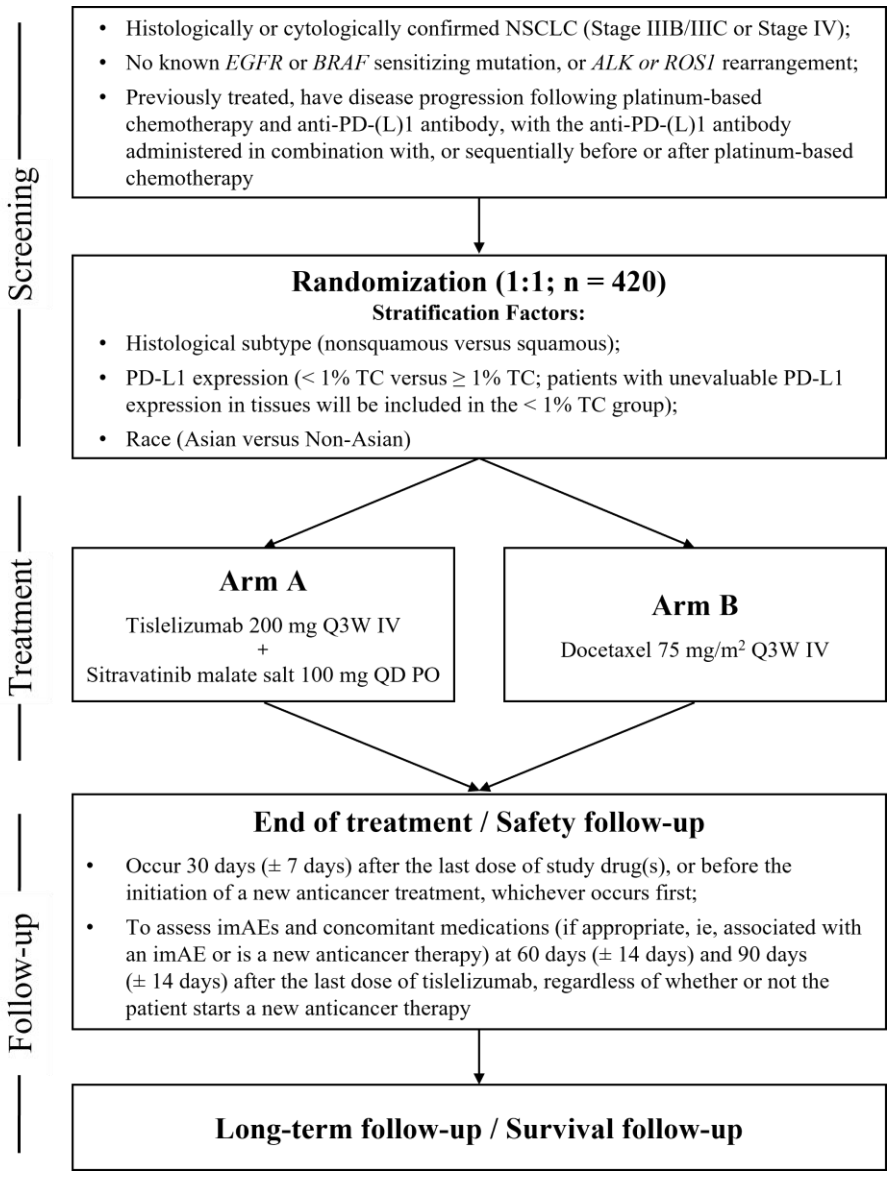
Patients with histologically or cytologically confirmed locally advanced or metastatic (Stage IIIB/IIIC or Stage IV) NSCLC who have disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy, are eligible. Histology of NSCLC will be confirmed at the investigator's site. Patients with known *EGFR* or *BRAF* sensitizing mutations, or *ALK* or *ROS1* rearrangement are ineligible for the study; for patients with nonsquamous NSCLC without tissue-based EGFR status, fresh or archival tumor tissues are required for *EGFR* mutation assessment. Archival tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. If archived formalin-fixed paraffin-embedded (FFPE) tissue is not sufficient for PD-L1 analysis, a fresh biopsy sample will need to be obtained. PD-L1 status will be determined by the percentage of TC with any

membrane staining (TC+) above background via the Ventana SP263 assay. Patients will be stratified by histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% TC versus ≥ 1% TC; patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group), and race (Asian versus non-Asian) to receive 1 of the following treatment regimens:

- Arm A: tislelizumab 200 mg intravenously once every 3 weeks in combination with sitravatinib 100 mg orally once a day;
- Arm B: docetaxel 75 mg/m^2 intravenously once every 3 weeks.

The study design schematic is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; imAE, immune-mediated adverse event; IV, intravenously; NSCLC, non-small cell lung cancer; PD-(L)1,

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programmed cell death protein-1/programmed cell death protein ligand-1; PO, orally; ROS1, ROS proto-oncogene 1; QD, once a day; Q3W: every 3 weeks; TC, tumor cells

For all study procedures, see Section 7 and Appendix 1 and Appendix 2.

3.2. Screening Period

Screening evaluations will be performed within 28 days of randomization. Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedure (see Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest Screening assessment results.

Archival tumor tissue must be collected for the purpose of PD-L1 analysis. If no archival samples are available, a fresh tumor biopsy at Screening is required. Refer to Section 7.7.1 for details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 1:1 ratio to receive either tislelizumab in combination with sitravatinib or docetaxel monotherapy. Randomization will be stratified according to histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% TC versus ≥ 1% TC; patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group), and race (Asian versus non-Asian), for 1 of the following treatment regimens:

- Arm A: tislelizumab 200 mg intravenously once every 3 weeks in combination with sitravatinib 100 mg orally once a day
- Arm B: docetaxel 75 mg/m^2 intravenously once every 3 weeks

Cycle 1 Day 1 will be defined as the first day the patient receives the study drug. A cycle is 21 days in length ± 3 days, unless a delay is medically necessary. A ± 3-day window is allowed for protocol-required assessments, unless otherwise specified. Tumor assessment will be conducted (by magnetic resonance imaging [MRI] and/or computed tomography [CT], with oral and/or intravenous contrast, unless contraindicated) during screening (within 28 days of randomization); every 6 weeks from Cycle 1 Day 1 (± 7 days) (at Weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter, until disease progression, withdrawal of consent, lost to follow-up, start of a new anticancer therapy, or death, whichever occurs earlier.

Patients in both arms will receive study treatment until disease progression, intolerable toxicity, death, or withdrawal of consent, whichever occurs earlier.

Patients will not be allowed to cross over to the other treatment arm. Tumor assessment and response will be determined by the IRC, who will evaluate disease progression and responses without the knowledge of randomization assignments, in accordance with RECIST v1.1. Details are provided in Section 7.5.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0) and laboratory results. Vital signs, physical examinations, ECOG PS changes, electrocardiogram (ECG) results, and other examinations will also be used for safety

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assessment. Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

In the event of unacceptable AEs potentially attributed to anti-PD-1 therapy and clearly not attributed to RTK inhibitor, sitravatinib can be continued as monotherapy at the discretion of the investigator. However, due to limited anticancer effect of rechallenging PD-(L)1 monotherapy after progression on PD-(L)1 inhibitor or PD-(L)1-inhibitor-based therapy, tislelizumab should not be used as monotherapy after permanent discontinuation of sitravatinib.

Response and disease progression will be assessed using RECIST v1.1. When disease progression is assessed by the investigator, the IRC is required to complete central image review and convey the results to the investigator as soon as possible. If disease progression is not confirmed by the IRC, it is recommended to continue the study treatment until disease progression is confirmed by the IRC if this is in the best interest of the patient as discussed with the medical monitor. In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for the IRC confirmation, the investigator should contact the medical monitor to inform him/her of the decision of treatment discontinuation.

A patient who discontinues study drugs early for reasons other than disease progression as assessed by the IRC (eg, toxicity, disease progression assessed by the investigator) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression per RECIST v 1.1 as assessed by the IRC, withdraws consent, is lost to follow-up, starts a new anticancer treatment, or until death, or until the study terminates, whichever occurs first.

In selected cases, patients in Arm A may continue treatment beyond radiologic progression if they continue to demonstrate clinical benefit; this decision will be at the discretion of the investigator and with the sponsor's agreement. The following criteria must be met in order to treat patients beyond progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention

Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

Patients who could benefit from study treatment in Arm A after disease progression as assessed by the investigator or IRC per RECIST v1.1 criteria may continue treatment until loss of clinical benefit as assessed by the investigator, withdrawal of consent, unacceptable toxicity, study completion by the sponsor, start of a new anticancer therapy, or death, whichever occurs first. Tumor assessment should continue as planned in patients receiving study treatment beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

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At the end of treatment or after treatment discontinuation, the date of progression, type and duration of subsequent therapies, response to subsequent therapy, date of progression on subsequent therapy, and survival data will be collected.

The duration of the study from the first enrolled patient to the final analysis for the primary endpoint OS is estimated to be approximately 32 months.

When a patient in Arm A reaches 2 years of treatment (as measured from Cycle 1 Day 1):

- Patients may continue on study therapy beyond 2 years if the investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study therapy beyond 2 years must be explicitly approved by the sponsor and will be contingent on the continued availability of tislelizumab and/or sitravatinib. The study assessment and procedure schedule will remain the same.
- Patients with confirmed CR, PR, or stable disease may stop treatment after 2 years if the patient wishes. The decision should be based on the investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. The investigator should notify the sponsor that treatment will be stopped before stopping the treatment. In these cases, the study assessments and procedures will be performed every 12 weeks (in conjunction with repeat radiographic imaging, as described in Section 7.5) rather than every cycle. If new information becomes available indicating the patient should restart treatment, the patient must sign a new ICF and meet (continued) treatment eligibility, and the investigator must receive approval before the patient can restart treatment.
  - If a patient has evidence of PD within 1 year of treatment interruption, the investigator can consider restarting tislelizumab and sitravatinib therapy (or sitravatinib alone) after discussion with the sponsor, contingent on the continued availability of the study drug(s).

3.4. End of Treatment/Safety Follow-up

The EOT Visit/Safety Follow-up is conducted when the investigator determines that the tislelizumab and sitravatinib combination or docetaxel monotherapy will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed ≤ 7 days before the EOT, these tests need not be repeated. Tumor assessment is not required at the EOT if ≤ 6 weeks have passed since the last assessment and should follow the regular schedule of assessment in Section 7.5. If the study drug(s) were initially interrupted due to AEs and then permanently discontinued, the EOT Visit may occur later, but no later than the permitted time of dose delay plus 7 days.

Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit (to occur 30 days [± 7 days] after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first). In addition, telephone contacts (safety follow-up phone call) with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected imAE at

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a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6.

Patients who discontinue study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.5.

See Appendix 1 for assessments to be performed at the EOT Visit/Safety Follow-up phone calls.

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3.5. Survival Follow-up

Patients will be followed for survival and to obtain information on subsequent anticancer therapy after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit or as directed by the sponsor until death, withdrawal of consent, lost to follow-up, or end of study.

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 3.5), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue study treatment for reasons which include, but are not limited to, the following:

- Disease Progression
- Adverse event
- Patient Decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

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3.6.2. Patient Discontinuation From Study (End of Study for an Individual Patient)

Patients may discontinue study for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Patients have completed all study assessments

3.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up. Alternatively, the end of study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory
- A rollover study becomes available

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit, and Safety Follow-up phone calls.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

At the end of study, any patients who, in the opinion of the investigator, continue to benefit from tislelizumab and/or sitravatinib at study termination will be offered the option to continue treatment in a company-sponsored clinical study until the loss of benefit, termination of the study by sponsor or the study drug(s) is commercially available in the country of the patient's residence.

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4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent if > 18 in the jurisdiction in which the study is taking place)
3. Metastatic or unresectable locally advanced histologically or cytologically confirmed NCSLC, not amenable to treatment with curative intent
4. Able to provide archival/fresh tumor tissues for biomarker analysis to assess PD-L1 expression and other biomarkers. Tumor tissues should be of good quality and acceptable sample type (see Section 7.7.1 for details). Written informed consent is required before performance of fresh tumor biopsies.
5. No known *EGFR* or *BRAF* sensitizing mutation, or *ALK* rearrangement or *ROS1* rearrangement
    a. Documentation of *EGFR* status with no sensitizing mutation by tissue-based test must be provided for patients with nonsquamous NSCLC before enrollment. For *EGFR* undocumented cases, archival or fresh tumor tissues are required for central assessment of *EGFR* mutation status. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at screening is mandatory. Written informed consent is required before performance of fresh tumor biopsies.
    b. Given that testing for *EGFR* mutation is not considered standard due to its low frequency in the squamous patient population (Chiu et al 2014), patients with squamous NSCLC and an unknown *EGFR* mutational status will not be required to be tested at screening.
    c. Patients with unknown *ALK* fusion oncogene or *ROS1* rearrangement status will not be required to be tested at screening given the low frequency in squamous and nonsquamous NSCLC.
6. Radiographic progression per RECIST v1.1 on or after anti-PD-(L)1-containing therapy for locally advanced and unresectable or metastatic NSCLC. If the anti-PD-(L)1-containing therapy is not the most recent systemic treatment, patients should also have radiographic progression per RECIST v1.1 on or after the most recent systemic treatment. Prior line(s) of treatment must include a platinum-based chemotherapy and an anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy. Patients must have received no more than 2 lines of prior systemic therapy for locally advanced and unresectable or metastatic disease.

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a. Adjuvant and neo-adjuvant chemotherapy will count as 1 prior line of chemotherapy if the disease progressed on or within 6 months after the completion of the last dose.

b. In locally advanced and unresectable NSCLC, disease progression on or within 6 months after the end of systemic therapy as part of prior curatively intended multimodal therapy will count as 1 prior line of systemic therapy. If chemoradiation is followed by planned systemic therapy without documented progression between the chemoradiation and systemic therapy, the entire treatment course counts as 1 line of therapy.

   Note: Patients who received anti-PD-(L)1 antibody as consolidation treatment following definitive chemoradiation for unresectable Stage III NSCLC can be enrolled immediately after disease progression, if the disease progression occurred within 6 months after the end of platinum-based chemotherapy component of the definitive chemoradiation.

c. Maintenance therapy following platinum-based doublet chemotherapy is not considered as a separate line of therapy.

d. No other prior immunotherapies with antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, including but not limited to anti-TIGIT, anti-OX40, and anti-CD137; prior anti-CTLA-4 used in combination with anti-PD-(L)1 is permitted.

e. No prior anticancer therapy having the same mechanism of action as sitravatinib (eg, tyrosine kinase inhibitor with a similar target profile or VEGF- or VEGFR inhibitor).

7. Criterion deleted

8. At least 1 measurable lesion as defined based on RECIST v1.1 by investigator

   Note: The target lesion(s) selected have not been previously treated with local therapy or the target lesion(s) selected that are within the field of prior local therapy have subsequently progressed as defined by RECIST v1.1.

9. Eastern Cooperative Oncology Group Performance Status ≤ 1

10. Adequate organ function as indicated by the following laboratory values (obtained ≤ 7 days before randomization):

    a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:

       i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

       ii. Platelets ≥ 100 x 10^9/L

       iii. Hemoglobin ≥ 90 g/L

    b. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 9)

    c. Urinary protein < 2+ by urine dipstick. If dipstick is ≥ 2+, then 24-hour urinary protein < 2 g per 24 hours.

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d. Aspartate aminotransaminase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN, or AST and ALT ≤ 5.0 x ULN for patients with documented liver metastases. If AST and/or ALT > 1.5 x ULN, alkaline phosphatase should be ≤ 2.5 x ULN.

e. Serum total bilirubin ≤ 1 x ULN.

f. International normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 x ULN.

g. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN.

11. Females of childbearing potential must be willing to use a highly effective method of birth control while on study treatment, and within 180 days after the last dose of study drug(s) and have a negative serum pregnancy test ≤ 7 days before randomization. See Appendix 10.

12. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 180 days after the last dose of study drug(s).

- A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
- Males with known “low sperm counts” (consistent with “subfertility”) are not to be considered sterile for purposes of this study.
- A nonsterile male that has a partner of non-childbearing potential may not be required to use highly effective method of birth control.

4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

1. Has received docetaxel as monotherapy or in combination with other therapies.
2. Squamous NSCLC with central cavitation, or NSCLC with hemoptysis (> 50 mL/day)
3. Patients with tumor shown by imaging to be located around important vascular structures or if the investigator determines that the tumor is likely to invade important blood vessels and may cause fatal bleeding (ie, radiologic evidence of tumors invading or abutting major blood vessels).
4. Active leptomeningeal disease for metastatic NSCLC, or uncontrolled or untreated brain metastasis.

   Note: Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all the following criteria:

   a. Brain imaging at screening shows no evidence of interim progression, clinically stable for at least 2 weeks and have no evidence of new brain metastases
   b. Measurable disease outside the CNS
   c. No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids for 3 days before randomization; anticonvulsants at a stable dose are allowed

d. No stereotactic radiation or whole-brain radiation within 14 days before randomization

5. Active autoimmune diseases or history of autoimmune diseases that may relapse.

   Note: Patients with the following diseases are not excluded and may proceed to further screening:

   a. Controlled Type I diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Celiac disease controlled by diet alone
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors

6. Any active malignancy ≤ 2 years before randomization except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)

7. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

   Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent) is permitted in the absence of active autoimmune disease
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption is permitted
   c. A brief course of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted

8. History of uncontrolled diabetes, or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management, or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization

9. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled lung diseases, including pulmonary fibrosis and acute lung diseases.

10. Severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy (not including antiviral therapy for hepatitis or HIV) within 14 days before randomization

11. Untreated HIV infection, if known. Patients with a known HIV infection are eligible if the following criteria are met:

    a. Stable on antiretroviral therapy for ≥ 4 weeks before randomization

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b. Patient agrees to adhere to antiretroviral therapy per World Health Organization (WHO) guidelines
c. No documented multidrug resistance that would prevent effective antiretroviral therapy
d. Viral load of < 400 copies per mL at screening
e. CD4+ T-cell count ≥ 350 cells/μL at screening
f. No history of an AIDS-defining opportunistic infection ≤ 12 months before randomization unless eligibility is agreed to by the medical monitor after consultation
g. If prophylactic antimicrobial drugs are indicated, patients may still be eligible upon agreement with the medical monitor

For sites in Germany, patients with a known history of HIV infection or if HIV status is unknown, a positive HIV test at screening are excluded

12. Untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV DNA ≥ 500 IU/mL or 2500 copies/mL, or active hepatitis C virus (HCV) carriers
Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or 2500 copies/mL) patients, and cured hepatitis C patients can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization.
13. Any major surgical procedure ≤ 28 days before randomization. Patients must have recovered adequately from the toxicity and/or complications from the intervention before randomization.
14. Prior allogeneic stem cell transplantation or organ transplantation
15. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Any history of acute myocardial infarction ≤ 6 months before randomization
    c. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV ≤ 6 months before randomization (Appendix 7)
    d. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
    e. Any history of cerebrovascular accident ≤ 6 months before randomization
    f. QT interval corrected by Fridericia's method (QTcF) > 470 msec

       Note: If a patient has QTcF interval > 470 msec on an initial ECG, a follow-up ECG will be performed to confirm the result.
    g. Cardiac left ventricular ejection fraction < 50% or lower limit of normal as assessed by echocardiography or multigated acquisition (MUGA). The same modality used at baseline must be applied for subsequent evaluations.
16. Patients with inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)

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17. Patients with hypersensitivity to tislelizumab, sitravatinib, docetaxel, to any ingredient in the formulation, or to any component of the container.
18. Patients who use anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring.
19. Within 4 weeks before randomization, patients with active bleeding disorder or any bleeding events ≥ CTCAE level 3, unhealed wounds, ulcers, or fractures
20. Patients with a history of artery/deep vein thrombosis within 6 months before randomization, such as cerebrovascular incident (including temporary ischemic attack), deep vein thrombosis, and pulmonary embolism
21. Received any Chinese herbal medicine or Chinese patent medicine for the treatment of NSCLC within 14 days before randomization, or received palliative radiation within 28 days before randomization for the lung or within 14 days before randomization for other organs.
22. Unacceptable toxicity on prior anti-PD-(L)1 treatment, defined as follows:
    a. ≥ Grade 3 AE related to anti-PD-1/PD-L1 treatment that did not respond to standard therapy and warranted treatment discontinuation.
    b. ≥ Grade 2 imAE associated with anti-PD-(L)1 unless the AE resolved or was well controlled by withholding the anti-PD-(L)1 treatment and/or treatment with steroids, with the exception of prior colitis, myocarditis, hepatitis, and pneumonitis, which are exclusionary.
    c. CNS or ocular AE of any grade related to anti-PD-(L)1.

    Note: Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.
23. Patient was administered a live vaccine ≤ 28 days before randomization.

    Note: Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
24. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct according to the investigator's judgement.
25. Concurrent participation in another therapeutic clinical study.

    Note: Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.
26. Unable to swallow capsules or with disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

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27. Patients with spinal cord compression due to metastatic disease not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that the disease has been clinically stable for > 2 weeks before randomization.
28. Criterion deleted
29. Prior randomization in a tislelizumab study regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out.
30. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities).
31. Women who are pregnant or are breastfeeding.
32. Known COVID-19 antigen positive by a licensed test during the screening period.
33. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention)

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5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap. Each vial is packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the tislelizumab IB for other details regarding tislelizumab.

5.1.2. Sitravatinib

Sitravatinib malate formulation will be provided as 50 mg and 35 mg capsules.

Sitravatinib drug product is packaged in 30-count, high-density polyethylene (HDPE), opaque white, round 75 cc bottles. A tamper-proof heat induction seal and a child-resistant closure are used.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label. Refer to the pharmacy manual for details regarding administration, accountability, and disposal. Please also refer to the sitravatinib IB for other details regarding sitravatinib.

5.1.3. Docetaxel

Docetaxel will be provided in vials for infusion.

The contents of the label will be in accordance with all applicable local regulatory requirements.

Management (ie, handling, storage, and disposal) of docetaxel will be in accordance with the relevant local guidelines and/or prescribing information.

Refer to the pharmacy manual for details regarding administration, accountability, and disposal.

5.2. Dosage, Administration, and Compliance

On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib should precede tislelizumab infusion. This order of dosing is important on days when blood sampling is scheduled for sitravatinib and M10 PK analysis.

Table 4: Selection and Timing of Dose for Each Patient

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Every 3 weeks	Intravenous	See Section 3.3
Sitravatinib	100 mg	Once a day	Oral	See Section 3.3
Docetaxel	75 mg/m^2	Every 3 weeks	Intravenous	See Section 3.3

5.2.1. Tislelizumab

Tislelizumab (200 mg) will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the pharmacy manual.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents if no symptoms are observed after the prior 2 treatment administrations.

The initial infusion (Cycle 1, Day 1) will be delivered over ≥ 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over ≥ 30 minutes if no symptoms are observed during the first treatment administration. Thirty minutes is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 8.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

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5.2.2. Sitravatinib

Sitravatinib will be administered orally at a dose of 100 mg, once a day, continuously.

The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken on an empty stomach (≥ 2-hour fast before each dose and no food for a minimum of 1 hour after each dose).
- Capsules should be taken with at least 200 mL (approximately 1 cup) of water.
- Patients should swallow the capsules whole and not chew them.
- If vomiting occurs after dosing, sitravatinib doses should not be replaced.
- If a patient forgets to take sitravatinib for more than 12 hours, he/she should skip the dose and resume taking the drug the next day.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

5.2.3. Docetaxel

Docetaxel will be administered by intravenous infusion at 75 mg/m^2 over 1 hour or according to institutional practices, every 3 weeks. Premedication with corticosteroids will be required in accordance with regional standards.

Before each cycle of docetaxel,

- Liver function tests (LFTs) should be reviewed, and docetaxel should not be given if bilirubin > 1 x ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN.
- Blood counts should be reviewed, and docetaxel should not be given if neutrophil counts are < 1500 cells/mm^3.

5.3. Overdose

5.3.1. Tislelizumab

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

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5.3.2. Sitravatinib

Any overdose or incorrect administration of sitravatinib should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect

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administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.3.3. Docetaxel

There is no known antidote for docetaxel injection overdosage. In case of overdose, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdose include bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic granulocyte colony-stimulating factor as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken as needed.

5.4. Study Drug Accountability

The study drugs required for completion of this study (tislelizumab, sitravatinib, and docetaxel) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of study drugs. Any damaged shipments will be replaced.

Accurate records of all study drugs received, dispensed, returned, and disposed of should be recorded on the site's Drug Inventory Log. Refer to the pharmacy manual for details of study drug management.

Compliance will be assessed by the investigator and/or appropriately delegated study personnel at each patient visit and through information provided by the patient. Patients enrolled in Arm A will be provided with patient diaries. The patient is responsible for maintaining the patient diary and will record the number of capsules of sitravatinib taken and if any were missed. The site personnel responsible for drug accountability will record the quantity of drug dispensed and quantity of drug received after the cycle visit. The patient diaries and the pharmacist record of the drugs will be assessed by the investigator/study personnel at each visit.

The investigator is responsible for tislelizumab and docetaxel reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain tislelizumab and docetaxel accountability records throughout the course of the study.

5.5. Dose Delay or Modification

A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion of tislelizumab, or docetaxel.

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

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5.5.1. Dose Delay or Modification for Tislelizumab and/or Sitravatinib

Patients may temporarily suspend 1 component of the study treatment or both, if they experience toxicity that is considered related to the study drug(s) and requires a dose to be withheld. Patients should resume study drug(s) as soon as possible after the AE(s) recover to baseline or Grade 1 (whichever is more severe) and within 4 weeks after the last dose of sitravatinib or within 12 weeks after the last dose of tislelizumab. Sitravatinib should be resumed at a reduced dose level as outlined in Table 5. If the administration of sitravatinib is interrupted for reasons other than sitravatinib-related toxicity, then treatment with the study drug(s) may be resumed at the same dose.

Table 5: Sitravatinib Dose Reductions

Dose Level 1	100 mg once daily
Dose Level -1	70 mg once daily
Dose Level -2	50 mg once daily [a]

[a] Dose reduction below 50 mg once daily may be undertaken after discussion with the sponsor.

The following dose delays or interruptions will be permitted:

- Sitravatinib can be interrupted for up to 28 consecutive days. If the treatment with sitravatinib is delayed for ≥ 14 days, then resumption at a reduced dose should be considered. If the drug is planned to be interrupted for > 28 days, the medical monitor should be contacted before permanent patient discontinuation from the study drug.
- Tislelizumab can be delayed or interrupted for up to 12 weeks.

Treatment intervals may be increased due to toxicity according to the dose modification guidelines. Cycle numbers will be counted based on the dosing of tislelizumab. For example, if the dosing of tislelizumab is delayed for 14 days, the next cycle can resume after an additional 21 days (ie, Day 35). Sitravatinib will be given continuously, unless interruption or discontinuation criteria are met.

If treatment intervals are increased, all procedures except imaging will be completed according to the cycle number, and not weeks on treatment. The tumor assessment schedule will not be altered even if the administration of study drug(s) is delayed.

If the patient is unable to resume sitravatinib and/or tislelizumab within the permitted timeframe after the last dose of study drug(s), then the patient should be discontinued from the study drug(s). Continuation/resumption of study drug(s) after an interruption of more than the permitted timeframe must be discussed with the medical monitor.

There will be no dose reductions for tislelizumab in this study. Dose reductions for sitravatinib are presented in Table 5. Once the dose has been reduced, re-escalation is not recommended.

In the event of unacceptable AEs potentially attributed to anti-PD-1 therapy and clearly not attributed to RTK inhibitor, sitravatinib can be continued as monotherapy at the discretion of the investigator. However, due to limited anticancer effect of rechallenging PD-(L)1 monotherapy after progression on PD-(L)1 inhibitor or PD-(L)1-inhibitor-based therapy, tislelizumab should not be used as monotherapy after permanent discontinuation of sitravatinib. When attribution to

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an unacceptable AE by either drug cannot be ruled out, both sitravatinib and tislelizumab should be held or the dose of sitravatinib should be reduced according to dose modification guidelines.

Based on the known toxicity profiles of sitravatinib and tislelizumab, certain AEs are likely to be associated with one drug versus the other. For example, treatment-emergent hypertension or palmar plantar erythrodysesthesia are likely to be associated with sitravatinib rather than tislelizumab; similarly, imAEs are likely to be associated with tislelizumab rather than sitravatinib. However, some drug-related AEs such as diarrhea and elevated liver function tests are overlapping. Therefore, it is crucial to fully evaluate each AE to confirm the etiology or exclude other causes in order to determine proper management of the adverse reaction and potential action regarding study treatment. The management guidelines for AEs of special interest for tislelizumab and sitravatinib-specific AEs are provided in detail in Section 8.8 and Section 8.9, respectively.

AEs (both nonserious and serious) associated with tislelizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment is critical to reduce complications. Tislelizumab must be withheld for drug-related severe or life-threatening AEs. See Appendix 8 for supportive care guidelines, including use of corticosteroids.

5.5.2. Dose Delay, Interruption or Modifications for Docetaxel

Guidelines for docetaxel dose modifications to manage general toxicities are shown in Table 6.

Table 6: Guidelines for Docetaxel Dose Modifications

Adverse event (Worst grade in previous cycle)	Action to be taken
Febrile neutropenia/Grade 4 AGC ≥ 7 days	Withhold docetaxel until symptoms resolve [a]
Grade 3/4 skin/ major organ/non hematologic toxicity	Reduce docetaxel to 75% of previous dose (eg, from 75 mg/m^2 to 55 mg/m^2) in the first episode; Discontinue treatment or reduce docetaxel to 75% of previous dose in the second episode; Discontinue treatment in the third episode.

Abbreviations: AGC, absolute granulocyte count.

[a] Do not re-treat until AGC ≥ 1.5 x 10^9, platelets ≥100 x 10^9, and docetaxel related toxicity ≤ Grade 1 except for alopecia or Grade 2 fatigue or laboratory abnormalities (For AST, ALT, or total bilirubin, please refer to Section 5.2.3 and Table 7).

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 (Grade 4) > 1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematologic toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and treatment then resumed at 55 mg/m^2. Should these AEs occur after the first dose reduction, then a second dose reduction is permitted. During this study, local standard practice for docetaxel administration may be used. Patients requiring more than 2 dose reductions of docetaxel due to adverse events should discontinue treatment with docetaxel. Patients who develop ≥ Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

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Guidelines for the management of hepatotoxicity for docetaxel-treated patients are shown in Table 7.

Table 7: Guidelines for Management of Hepatotoxicity in Patients Receiving Docetaxel

	AST/ALT		Alkaline phosphatase		Total bilirubin	Docetaxel dose
Mild to moderate	> 1.5x ULN	and	> 2.5 x ULN		NA	75%
Severe	> 3.5 x ULN[a]	and	> 6 x ULN	OR	> 1.5x ULN[b]	Do not treat. Discontinue treatment if it is already started.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; ULN, upper limit of normal.
[a] > 5 x ULN if liver metastasis exists;
[b] > 3 x ULN if Gilbert Syndrome or indirect bilirubin proven to be extrahepatic

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6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

All prior therapies, their dates of administration, best responses, and dates of progression for NSCLC will be collected at study entry.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals) and in a patient's interest are allowed.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 30 days before randomization will be recorded.

Opiates and other medications required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

6.2.1.1. Systemic Corticosteroids

Systemic corticosteroids given to control imAEs must be tapered gradually (see Appendix 8) and be administered at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

6.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL or 2500 copies/mL at Screening, must initiate treatment 2 weeks before randomization and continue until 6 months after the last dose of study drug(s). Patients should continue effective antiviral treatment during the study to decrease potential viral reactivation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel 2015). The investigator may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL or 2500 copies/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before randomization and continue treatment during the study, and for 6 months after the last dose of study drug(s).

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6.2.1.3. Radiation Therapy

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeated imaging demonstrates no new sites of bone metastases.
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1.
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per investigators' discretion. The medical monitor should be informed of the on-study radiotherapy. These patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

Withhold of study treatment is required during palliative radiotherapy.

6.2.2. Prohibited Concomitant Medications/Procedures

Live vaccines ≤ 28 days before randomization for patients in both arms, during tislelizumab treatment and ≤ 60 days after the last dose of tislelizumab for patients in Arm A are prohibited.

The following medications are prohibited during Screening and through the EOT/Safety Follow-up Visit:

- Any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China National Medical Products Administration (NMPA) for use as anticancer treatment (regardless of cancer type)
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin)

Patients must notify the investigator of all herbal remedies used during the study.

6.2.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

Arm A:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment

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Arm A and Arm B:

- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.1.3.
- Surgeries, except:
  - To treat an AE (eg, appendectomy)

  In the event that major surgery is needed during study treatment, the patient should, if possible, interrupt dosing with study treatment 2 weeks in advance of the surgery and may resume dosing 2 weeks after the surgery.

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

Potential Interaction of Docetaxel With CYP3A4 inhibitors

Docetaxel is a cytochrome P450 3A4 (CYP3A4) substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided (examples listed in Appendix 11).

Potential Interaction of Sitravatinib With CYP Enzyme Inhibitors/Substrates

Sitravatinib is not considered a high-risk compound as a victim of drug-drug interaction (DDI) because multiple enzymes, including CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4 are involved in its metabolism.

In vitro, sitravatinib showed direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (Section 1.5.1). Concomitant medications that are sensitive substrates or substrates with a narrow therapeutic index for these CYP enzymes (examples listed in Appendix 11) should be avoided during sitravatinib treatment.

Potential Interaction of Sitravatinib With Transporter Inhibitors/Substrates

Sitravatinib was identified to be a substrate of P-gp and inhibitor of both P-gp and BCRP (Section 1.5.1). Inhibitors of P-gp (eg, clarithromycin, itraconazole, propafenone, quinidine, ranolazine, ritonavir, verapamil) may increase sitravatinib exposure while inducers of P-gp (eg, rifampin) may decrease sitravatinib exposure. Concomitant medications that inhibit or induce P-gp should be avoided when administering sitravatinib to patients. Concomitant medications

that are sensitive substrates or substrates with narrow therapeutic indices for P-gp and/or BCRP transporters (examples listed in Appendix 11) should be avoided during sitravatinib treatment.

Sitravatinib With Medications That Prolong QT/QTc

Per the International Council for Harmonisation (ICH) E14 guidance, it is recommended to avoid medications with the potential to prolong QT/QTc intervals or cause Torsades. Please refer to Appendix 11 for a list of medications or substances to be avoided or used with caution during treatment with sitravatinib.

Potential Interaction of Sitravatinib With Tislelizumab

Sitravatinib administered in combination with tislelizumab is unlikely to result in clinically relevant DDI based on the characteristics of absorption, metabolism, elimination, or protein binding. Tislelizumab is a monoclonal antibody and is administered intravenously, whereas sitravatinib is a small molecule therapeutic administered orally. No absorption interactions are expected. No studies on the metabolism of tislelizumab have been reported in vitro or in humans. Like most therapeutic proteins, tislelizumab is not expected to be metabolized by liver cytochrome P450 (CYP) or other drug-metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

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7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments is provided in Appendix 1 and Appendix 2. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening

Screening evaluations will be performed within 28 days before randomization. Patients who agree to participate will sign the ICF before undergoing any screening procedure. The screening period begins on the first day a screening procedure is conducted. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests, unless otherwise indicated. If laboratory tests at Screening are performed within 7 days before randomization, these tests (hematology, clinical chemistry, urinalysis, coagulation and pregnancy test) do not have to be repeated and must be reviewed before randomization.

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.7) sections. The PK sampling schedule is shown in Appendix 2.

Rescreening under limited conditions may be allowed after consultation with BeiGene, eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. Informed consent forms for enrolled patients and for patients who are screened but not enrolled will be maintained at the study center.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.2. Patient Numbering

After obtaining informed consent, study personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant.

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7.2. Enrollment

7.2.1. Confirmation of Eligibility

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with the International Council for Harmonisation (ICH) E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

7.2.2. Randomization

Site personnel will access the IRT system to randomize treatment assignment and to assign the study drug. Study treatment must commence within 2 business days after randomization/treatment assignment.

7.3. Tislelizumab, Sitravatinib, and Docetaxel Dispensation

Tislelizumab, sitravatinib, and docetaxel will be dispensed and administered as described in Section 5.2. On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib should precede tislelizumab infusion.

7.4. Safety Assessments

7.4.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected while the patient is in a seated or supine position after resting for 10 minutes.

The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and within 30 minutes after the infusion. Vital signs should also be recorded before administration of sitravatinib; recorded values may be used for pre-tislelizumab assessment if vital signs are collected within 60 minutes before tislelizumab infusion.

7.4.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted including evaluations of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v5.0 and recorded on the eCRF with appropriate disease/condition terms.

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At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 4) will be assessed during the study.

7.4.4. Laboratory Safety Tests

Local and/or central laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3.

If laboratory tests at screening are performed within 7 days before randomization, these tests (hematology, clinical chemistry, coagulation, urinalysis, and pregnancy test, if applicable) do not have to be repeated and the test results must be reviewed before the first dose of study drug(s). Hematology and serum chemistry (including liver function tests) as specified in Appendix 3 should be performed at each cycle for both arms. Additional laboratory tests are required weekly for patients in Arm A in Cycle 1 and Cycle 2.

After Cycle 1, laboratory tests can be performed up to 2 days before Day 1 of subsequent cycles and results are to be reviewed within 48 hours before study drug administration. Coagulation tests as specified in Appendix 3 are required at Screening and subsequently as clinically indicated. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. Urinalysis will be performed on Cycle 1 Day 1 (if not done within 7 days before randomization) and subsequently as clinically indicated.

Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days before randomization. Urine or serum pregnancy tests will be performed once every 3 weeks during treatment before administration of study drug(s) at each cycle and at the EOT Visit. A negative pregnancy test must be completed and recorded before administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

Thyroid assessments will be performed at screening, every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the EOT Visit, as specified in Appendix 1.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decisions.

7.4.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and CK cardiac isoenzyme (CK-MB) is monitored in all tislelizumab studies to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 8 for guidelines for management of

suspected immune-mediated myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.4.5. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

For patients in Arm A, ECG assessments will be performed at pre-dose (within 30 minutes before pre-dose PK sample collection of sitravatinib) and approximately 6 hours post dose (within 30 minutes before post-dose PK sample collection of sitravatinib) on Cycle 1 Day 1 and Cycle 2 Day 1. For other ECG assessments, when coinciding with blood draws at the same timepoint, ECG assessment should be performed either before blood draws, or at least 30 minutes after blood draws. Patients should rest in semirecumbent supine position for at least 10 minutes before ECG collection. If an ECG has been performed within 7 days before randomization (for patients in Arm B) or before the EOT visit (for all patients), the test does not need to be repeated on Cycle 1 Day 1, and the EOT visit, respectively. ECG collection may be done at other timepoints as clinically indicated.

7.4.6. Multigated Acquisition Scans or Echocardiograms

Evaluations of cardiac function will be performed at screening and every 12 weeks (± 7 days). Evaluation by echocardiogram is preferred. Evaluation by MUGA scan is an acceptable alternative if necessary. The method used for individual patients should be consistent throughout the study.

7.4.7. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.4.8. Hepatitis B, Hepatitis C, and HIV Testing

Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody). Viral load assessment (HBV DNA and HCV RNA) will be performed if the HBsAg and/or HCV antibody test is positive. HIV serology is required at screening for patients in Germany with an unknown HIV status and will include antigen and/or antibodies. Viral load assessment (HIV RNA) and CD4+ T-cell count tests will be conducted at screening for patients outside Germany with a known HIV infection.

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before randomization and while on study, approximately every 6 weeks (± 7 days) from Day 1 of Cycle 1 in the first 12 months and approximately every 9 weeks (± 7 days) thereafter, based on RECIST v1.1. Results of standard-of-care tests or examinations performed before obtaining informed consent and

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≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule.

Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral and/or intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments.

All measurable and nonmeasurable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening is required to be used throughout the study (eg, the same contrast protocol for CT scans).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed within 28 days before randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a complete response (CR) is suspected in target lesion or when progression in bone is suspected.
  - If bone metastases are visualized on the bone scan or PET scan at screening, a confirmatory CT/MRI scan should be performed. If the metastases are confirmed by CT/MRI, then evaluation by CT/MRI should be given preference for subsequent assessments. If the metastases are not confirmed by CT/MRI, then the use of bone scan or CT/MRI for subsequent assessments is at the investigator's discretion.
  - If an increase in the uptake of existing lesions is seen on a bone scan, or the appearance of new osteoblastic bone lesions is seen on an x-ray, CT, or MRI, this should not automatically be considered evidence of progression in an otherwise stable or responding subject. It may in fact be indicative of response to therapy.
  - New areas of uptake seen on a bone scan should not automatically result in diagnosis of progressive disease but should be correlated with other available imaging (eg, CT, MRI, or x-ray).
- CT scans of the neck or extremities should be performed at Screening only if clinically indicated and should be repeated throughout the study if there is evidence of metastatic disease in these regions at Screening.
- At the investigator's discretion, other methods of assessing target lesions and nontarget lesions per RECIST v1.1 may be used. However, CT or MRI should be given preference for assessment of target lesions.

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Response will be assessed by the IRC and the investigator using RECIST v1.1 (see Appendix 5). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur 4 weeks or later after the first response or at the next scheduled assessment timepoint.

After disease progression is assessed by the investigator or IRC per RECIST v 1.1, and at the investigator's discretion, a patient that would continue to benefit from the study treatment in Arm A may continue their assigned treatment.

The following criteria must be met in order to treat patients who may continue to benefit from the study treatment in Arm A after disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that they may be forgoing treatment that has shown benefit by continuing treatment beyond progression.
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

Response and PD will be assessed using RECIST v1.1. When PD is assessed by the investigator, the IRC is required to complete central image review and convey the results to the investigator as soon as possible. If PD is not confirmed by IRC, it is recommended to continue study treatment until PD is confirmed by IRC, if this is in the best interest of the patient as discussed with the medical monitor. In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for IRC confirmation, the investigator should contact the medical monitor to inform him/her of the decision of treatment discontinuation.

Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity, PD by the investigator) will continue to undergo tumor assessments following the original plan until the patient, experiences disease progression per RECISTv1.1 assessed by the IRC, withdraws consent, is lost to follow-up, starts a new anticancer treatment, until death, or until study termination, whichever occurs first.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. That is, they should not be adjusted for delays in cycles.

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7.6. Pharmacokinetic and Antidrug Antibody Testing

The PK concentrations will be determined using plasma (sitravatinib and its active metabolite M10) or serum (tislelizumab) samples collected at specified timepoints within a reasonable variation window (refer to Appendix 2). As sitravatinib malate capsule is an alternative formulation previously not evaluated in patients, intensive PK samples for sitravatinib and M10 will be collected in 12 patients (6 from China and 6 from ex-China) according to the chronological order during enrollment in Arm A if patients agree, while sparse samples will be collected from the remaining patients in Arm A. For tislelizumab, sparse samples will be collected from patients who received tislelizumab treatment (Arm A). The actual time of each sample collection will be recorded on the source document and CRF. An additional sitravatinib PK blood sample may be drawn before a daily sitravatinib dose at a clinic visit at least one week following a dose modification of sitravatinib, or as soon as possible after a serious AE.

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (refer to Appendix 2). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program.

The following assessments will be performed at a bioanalysis laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay
- Tislelizumab PK assay: serum samples will be assayed for tislelizumab concentrations using a validated immunoassay
- Sitravatinib PK assay: plasma samples will be assayed for sitravatinib concentrations using a validated LC-MS/MS method.
- M10 PK assay: plasma samples will be assayed for M10 concentrations using a validated method.

Shipping, storage, and handling of samples for the PK and ADA assessment will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.7. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

7.7.1. Tissue Biomarkers

See Appendix 1 for the tissue biomarker sample collection schedule.

Archival tumor tissues (FFPE blocks or approximately 15 [at least 5 slides for PD-L1 assessment] freshly cut unstained FFPE slides from each block) must be collected (if available) for biomarker analysis to assess PD-L1 expression (mandatory) and, if tissue samples are

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sufficient, to assess biomarkers such as GEP, DNA alteration, tTMB and MSI (optional). Tissues for optional biomarker analysis can be retrospectively provided after relative regulation approval, eg, regulations on the management of Human Genetic Resource Administration of the People's Republic of China (HGRAC). Submission of < 15 unstained slides is not a protocol deviation. If no archival tumor tissues can be provided, a fresh biopsy is mandatory during screening for PD-L1 assessment. For nonsquamous NSCLC, documentation of *EGFR* status with no sensitizing mutation by tissue-based test must be provided before enrollment. For undocumented cases, additional archival or fresh biopsy tumor tissues (FFPE blocks or approximately 3 freshly cut unstained FFPE slides from each block) will be required for central assessment of *EGFR* mutation status during screening.

Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration, brushing, cell pellets from pleural effusion, lavage samples, and bone/bone marrow aspirates are not acceptable. Written patient consent is required for fresh tumor biopsies.

In addition to archival tumor tissues, fresh biopsies from an accessible tumor site(s) at screening (within 28 days before randomization) and/or at the time of confirmed PD are recommended to explore response or resistance mechanisms. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy.

7.7.2. Blood Biomarkers

See Appendix 1 for the blood biomarker sample collection schedule.

Peripheral blood samples will be collected for biomarker analysis, such as DNA alteration, bTMB, MSI and ctDNA. Approximately 10 mL of peripheral blood samples will be collected at baseline (pre-dose on Cycle 1 Day1) and pre-dose on Cycle 3 Day 1. For patients who have confirmed CR/PR (± 14 days) or confirmed PD, additional blood samples (approximately 10 mL) will be collected upon each confirmation. Written patient consent is required for blood sample collections.

7.8. Patient-Reported Outcomes

Patients will be asked to complete PRO questionnaires before any clinical activities (including blood draws or imaging scans) are performed during on-study clinic visits according to the schedule in Appendix 1.

The PRO questionnaires include the European Organisation for Research and Treatment of Cancer (EORTC) core cancer (QLQ-C30) and its lung cancer module QLQ-LC13, as well as the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) (Appendix 12, Appendix 13, and Appendix 14).

The PROs are to be completed on Cycle 1 Day 1 before any assessments, then coincide with disease evaluations and continue at the same intervals until the start of subsequent therapy; if the disease evaluation does not coincide with a clinic visit, the PRO assessments should be completed at the clinic visit closest to the disease evaluation.

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7.9. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). In Cycle 1 and Cycle 2, all the patients in Arm A will return for assessments on Day 8 (± 1 day) and Day 15 (± 2 days). Sitravatinib will be given in the clinic.

All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed before study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed before dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of the previous cycle.

7.10. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/focused physical examination; ECOG Performance Status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

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8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Risks Associated With Study Drug

8.1.1. Risks Associated With Tislelizumab and Sitravatinib

Tislelizumab and sitravatinib are investigational agents that are currently in clinical development. Across studies, the safety profile of tislelizumab is consistent with the therapeutic class of the drug. When combined with another investigational agent, the safety profile of the combination is generally consistent with the safety profiles of each drug given as monotherapy.

Limited safety data for sitravatinib in combination with tislelizumab in patients are available, and the full safety profiles have not been characterized. The following recommendations are based on results from nonclinical and clinical studies with tislelizumab or sitravatinib and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.8.3.

The guidelines for management of potential AEs more specific to treatment with sitravatinib or agents in the same class of cancer treatment are presented in Section 8.9.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 8.

8.1.2. Risks Associated with Docetaxel

Please refer to Table 8 for the reported toxicities of docetaxel. Because of the ethanol content in the docetaxel formulation, some patients may experience intoxication during and after treatment that should be monitored (and infusion rate decreased if appropriate). The investigator should refer to the prescribing information for a complete list of potential side effects.

Table 8: A Summary of the Commonly Reported Toxicities of Docetaxel

Most common side effects	Less common side effects (but may be severe or life-threatening
• Myelosuppression ± infection or bleeding (may be severe) • Hypersensitivity (may be severe) • Fluid retention (may be severe) • Neuropathy (may be severe) • Cutaneous effects (including nails, may be severe) • Alopecia	• Secondary malignancy/leukemia • Cardiotoxicity, arrhythmia • Pneumonitis • Gastrointestinal obstruction, perforation, hemorrhage • Venous thromboembolism • Arterial thromboembolism

• Gastrointestinal (anorexia, nausea, vomiting, stomatitis, diarrhea, constipation) • Asthenia (may be severe)	• Disseminated intravascular coagulation • Seizures • Hepatotoxicity

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies of sitravatinib and tislelizumab and clinical data with sitravatinib and tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before randomization are excluded from the study. Patients with contraindications for docetaxel treatment are also excluded from the study (see Section 4.2 for the full list of exclusion criteria).

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 9), physical examinations, laboratory measurements (hematology, chemistry, etc) and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, study drug(s) will only be administered after clinical laboratory results have been reviewed. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2.1).

Serum samples will be drawn for determination of ADAs to tislelizumab in patients randomized to the tislelizumab arm, if treatment assignment is known. Otherwise, samples will be drawn from all randomized patients but will only be analyzed in patients treated with tislelizumab.

All AEs will be recorded during the study (AE from the time of the first dose of study drug(s) and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-mediated AEs will be recorded until up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

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Investigators are instructed to report all AEs (including pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 8.7.

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug administration, even though the condition may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

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Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the tislelizumab IB, sitravatinib IB, and prescribing information for docetaxel (TAXOTERE prescribing information) in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor, because the causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as “related” or “not related” based on all information available at the time of reporting. An AE is considered related if there is “a reasonable possibility” that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered “related” to study drug if any of the following criteria are met, otherwise the event should be assessed as “not related”:
  - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
  - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
  - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient’s clinical condition or other concomitant AEs).

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8.3.4. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count [CBC], coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity
  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent 1 of the outcomes listed above)

The following are NOT considered to be SAEs:

- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the IB.

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8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug(s) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 9. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.1.

Table 9: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs [a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 10.

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Table 10: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial/follow-up [a] report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	Electronic submission of SAE form to safety portal [b]

Abbreviations: EDC, electronic data capture; SAE, serious adverse event.
[a] Report follow-up information that is clinically relevant and pertaining to the SAE which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to each study drug. Follow-up information will also be reported at the discretion of the investigator if the new or updated information changes the medical assessment of the case.
[b] SAE reports should be submitted to the sponsor safety database electronically from within the EDC. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for tislelizumab, sitravatinib, and docetaxel studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised IB) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

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8.6.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.6.4. Disease Progression

Disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an AE (eg, “death,” “death of unknown cause,” or “death unexplained”).

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 180 days after the last dose of study drug(s), a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

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8.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information (RSI) documents:

- Tislelizumab IB
- Sitravatinib IB
- Prescribing information for docetaxel

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.8.3) should be classified as imAEs and identified as such in the eCRF AE page.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

An extensive list of potential imAEs appears in Table 12. All conditions similar to those listed should be evaluated to determine whether they are imAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 8.

8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include, but are not limited to, fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Sign and symptoms should be reported as the AE term(s).

8.7. Management of Adverse Events Potentially Associated With Either or Both of Sitravatinib and Tislelizumab

Based on the known toxicity profiles of sitravatinib and tislelizumab, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, palmar plantar erythrodysesthesia, and hemorrhagic events are known risks for sitravatinib treatment, while imAEs are risks for tislelizumab treatment. However, certain AEs may be initially considered attributed to either study drugs, such as diarrhea, hypothyroidism, and liver enzyme elevation. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management.

If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting or holding both drugs, initiating treatment with a corticosteroid (with exception of hypothyroidism, type I diabetes mellitus) to treat an imAE, and other supportive care should be taken promptly.

8.8. Management of Adverse Events of Special Interest of Tislelizumab

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a minimum of a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined below.

8.8.1. Managing Infusion-Related Reactions

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) is provided in Table 11.

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Table 11: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Tislelizumab

NCI-CTCAE grade	Treatment modification for tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions and be administered with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from tislelizumab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted as indicated per the type of reaction. This includes, but is not limited to, an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

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NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes, but is not limited to, oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.8.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be immediately stopped and the patient discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress, laryngeal edema, and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The patient should then be placed on a monitor immediately, and an ICU should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs infusion. Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

8.8.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include, but are not limited to, serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out; the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy; and is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 12. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-mediated.

Recommendations for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017, Brahmer et al 2018), and common immune-mediated toxicities are detailed in Appendix 8. For any AEs not included in Appendix 8, please refer to the ASCO

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Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 12: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barré syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommendations for managing imAEs are detailed in Appendix 8.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade after restart of study drug should permanently discontinue treatment.

8.9. Management of Sitravatinib-specific Adverse Events

8.9.1. Management of Non-Hematological Toxicities of Sitravatinib

Patients experiencing symptomatic Grade 2 non-hematological sitravatinib-related AEs should have a dose reduction to the next lower dose level at the discretion of the investigator, per the reduction schedule (Table 13). Dose reductions are expected to improve treatment tolerability.

Non-hematological toxicities ≥ Grade 3 considered to be related to sitravatinib treatment are to be managed with sitravatinib interruption, until resolution of toxicity to ≤ Grade 1 or to baseline value. In the case of Grade 3 or 4 electrolyte abnormalities that are not clinically complicated and that resolve spontaneously or with conventional medical treatment within 72 hours, or Grade 3 asymptomatic amylase or lipase elevation, treatment can be resumed at the same dose; if not, treatment should be resumed at a reduced dose as outlined in Table 13. Recurrence of the

toxicity is managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

Table 13: Sitravatinib Dose Modifications – Non-Hematological Drug-Related Toxicities

Toxicity	Treatment delay	Dose modification
Grade 1	Not required	
Grade 2 - Asymptomatic	Implemented based on investigator and patient discretion	
Grade 2 - Symptomatic	Implemented based on investigator and patient discretion	Dose reduction to next lower dose level
Grade 3 or 4	Hold until ≤ Grade 1 or return to baseline	Resume at dose one or more levels below that inducing the toxicity. Exceptions are presented in footnotes

Notes:
1. Management of specific adverse events (eg, hypertension) for sitravatinib are presented in sections below.
2. Patients may resume at the same dose in the following cases:
   - Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours
   - Grade 3 amylase or lipase elevation that is not associated with the symptoms or the clinical manifestations of pancreatitis

8.9.2. Management of Hematological Toxicities of Sitravatinib

Hematological toxicities are not a frequent cause of treatment interruption or discontinuation of sitravatinib treatment. Observed ≥ Grade 3 hematological events that are considered to be causally related to sitravatinib should initially be managed using treatment interruption. In addition, dose reduction of sitravatinib will be implemented at the discretion of the investigator in the following cases:

- Grade 3 or 4 febrile neutropenia
- Grade 4 neutropenia persisting for ≥ 8 days
- Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding

8.9.3. Dose Modification Guidelines for Sitravatinib-Specific AEs

Dose modification guidelines for increased blood pressure, increased hepatic transaminase not likely to be immune-mediated, and palmar-plantar erythrodysesthesia (PPE) are presented in Table 14, Table 15, and Table 16, respectively. Guidance for management of Hy's Law cases is also provided below. Additional management guidelines for sitravatinib-specific AEs are also described below.

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Table 14: Sitravatinib Dose Modification for Increased Blood Pressure

Toxicity	Drug interruption	Dose modification
Grade 1 or 2 hypertension	Not required	
Grade 3 hypertension without clinically significant increases in BP as defined below	Implemented based on investigator discretion Consider antihypertensives per Section 8.9.4	
Grade 3 hypertension with clinically significant increases in BP *defined as* either an increase of ≥ 30 mm Hg in systolic BP to ≥ 180 mm Hg *or* increase of ≥ 20 mm Hg in diastolic BP to ≥ 110 mm Hg, confirmed with repeated testing after ≥ 5 minutes	Hold until ≤ Grade 2 or return to baseline	Dose reduction to next lower dose level
Grade 4 hypertension	Discontinue sitravatinib	Discontinue sitravatinib

Abbreviation: BP, blood pressure.

For cases where transaminase increases are not likely to be immune-mediated, treatment management decisions are to be made per investigator's discretion in consideration of clinical factors. Recommended treatment modifications for sitravatinib are provided in Table 15.

Table 15: Sitravatinib Dose Modification for Increased Hepatic Transaminase

Toxicity	Drug interruption	Dose modification
Grade 1 (> ULN to 3.0 x ULN)	Not required	
Grade 2 (> 3.0 to 5.0 x ULN)	Hold until ≤ Grade 1 or return to baseline	Decrease by 1 dose level
Grade 3 or 4 (> 5.0 x ULN)	Hold until ≤ Grade 1 or return to baseline	If resolution occurs within 22 days, decrease by 1 dose level. If no resolution within 22 days, discontinue sitravatinib.

Abbreviation: ULN, upper limit of normal.

Table 16: Sitravatinib Dose Modification for Palmar-Plantar Erythrodysesthesia

Toxicity*	Treatment Delay	Dose Modification
Grade 1	Not required	Not required
Grade 2	Based on investigator discretion	Dose reduction to the next lower level
Grade 3	Hold until ≤ Grade 1 or return to baseline	Resume at dose one or more levels below that inducing the toxicity

Abbreviation: PPE, palmar-plantar erythrodysesthesia.

*For any event of PPE, regardless of severity, patients are to be counseled on measures to mitigate the effects of PPE, including avoidance of exposure of hands and feet to hot water, other sources of heat, activities that cause unnecessary force or friction (rubbing), chemicals (eg, cleaning products), and wearing well-ventilated shoes or clothing. Treatment may include topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams.

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8.9.3.1. Management of Hy's Law Cases

In the event a patient develops concurrent increase in AST and/or ALT ≥ 3 x ULN, and bilirubin ≥ 2 x ULN but without concurrent increases in alkaline phosphatase (ie, alkaline phosphatase < 2 x ULN) that is not attributable to liver metastases or biliary obstruction, sitravatinib and tislelizumab should be permanently discontinued and steroids administered.

8.9.4. Hypertension

Hypertension, including Grade 4 events, has been reported with sitravatinib. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine should be considered if antihypertensive therapy is required and should be considered for patients with Grade 3 hypertension without clinically significant increases in blood pressure (BP) (see Table 14). In cases of Grade 3 hypertension with clinically significant increases in blood pressure, sitravatinib dosing should be hold until resolution of hypertension to ≤ Grade 2 or to baseline. Treatment with sitravatinib should resume at a lower dose at the discretion of the investigator. If significant hypertension recurs, options include a change in medical management of the patient, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the investigator. In the event of Grade 4 hypertension, sitravatinib will be permanently discontinued (see Table 14).

8.9.5. Palmar-Plantar Erythrodysesthesia

PPE syndrome has been reported as a DLT in the Phase 1 study of sitravatinib. Measures that can be taken to manage the syndrome include avoidance of exposure of hands and feet to hot water when washing dishes or bathing, or to other sources of heat; avoidance of activities that cause unnecessary force or friction (rubbing) on the hands or feet; avoiding contact with harsh chemicals such as cleaning products; use of tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers, and wearing of loose fitting, well-ventilated shoes and clothes. Treatment may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams. In more severe cases, dose interruption and reduction may be warranted (See Table 16).

8.9.6. Diarrhea

Diarrhea has been reported with sitravatinib treatment, though the mechanism remains unclear, as with other small molecule RTK inhibitors. Patients should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled. Investigators should also evaluate whether diarrhea may be attributable to the imAE of colitis.

The presence of abdominal pain, mucus or blood in the stool, or peritoneal signs should raise the index of suspicion for immune-mediated colitis, as these features are generally not observed with sitravatinib treatment-associated diarrhea. The diarrhea observed with sitravatinib generally improves within several days of interrupting study medication, and close observation may help establish the most likely causality.

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8.9.7. Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib is unknown; however, such events have been reported with inhibitors of VEGFR. Patients with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and suspension of treatment is to be implemented for patients developing clinically significant bleeding.

8.9.8. Thrombotic Events

Though thrombotic events (eg, pulmonary embolism) have been reported with sitravatinib and with inhibitors of VEGFR, the risk of such events with sitravatinib is unknown. Precautions should be taken in patients with recent, clinically significant thrombotic events, and treatment is to be discontinued in patients who develop clinically significant thromboembolic complications such as acute myocardial infarction or severe pulmonary embolism.

8.9.9. Thyroid Dysfunction Other Than Immune-Mediated

Hypothyroidism and increases in thyroid-stimulating hormones have been reported in patients taking sitravatinib. Patients diagnosed with hypothyroidism should be treated with hormone replacement therapy and may continue treatment with sitravatinib at the investigator’s discretion.

8.9.10. Decreased Left Ventricular Ejection Fraction

Decreased left ventricular ejection fraction has been reported with sitravatinib. In addition, decreases of left ventricular ejection fraction to < 50% on-study were observed in patients undergoing scheduled MUGA scans or echocardiograms. The dose of sitravatinib should be interrupted and/or reduced in patients with an ejection fraction < 50% and > 20% below baseline. Discontinuation should be considered for patients requiring acute hospitalization for treatment of congestive heart failure.

8.9.11. Proteinuria

Although the risk with sitravatinib is unknown, proteinuria has been described with other inhibitors of the VEGFR pathway. Patients who develop ≥ 2+ proteinuria should undergo 24-hour urine collection for assessment of urine protein; treatment with sitravatinib should be discontinued in the presence of ≥ 2 grams of urine protein/24 hours and may restart when protein levels decrease to less than 2 grams/24 hours. Patients who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

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9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the data collection is completed and the database is locked and released. Details of the statistical analyses will be included in a separate SAP.

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.2.2, patients will be randomized using the IRT system for this study by permuted block stratified randomization with stratification factors of histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% TC versus ≥ 1% TC; patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group), and race (Asian versus non-Asian). There are 2 treatment arms. Patients will be randomized 1:1 to receive tislelizumab in combination with sitravatinib or docetaxel monotherapy.

9.1.2. Analysis Sets

The Intent-to-Treat (ITT) Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arms. This will be the primary analysis set for all efficacy analyses.

The Safety Analysis Set includes all patients who received ≥ 1 dose of any of the study drugs; it will be the analysis set for the safety analyses.

The Sitravatinib PK Analysis Set includes all patients in the Safety Analysis Set who contributed ≥ 1 quantifiable postbaseline PK sample for sitravatinib.

The M10 PK Analysis Set includes all patients in the Safety Analysis Set who contributed ≥ 1 quantifiable postbaseline PK sample for M10.

The Tislelizumab PK Analysis Set includes all patients in the Safety Analysis Set who contributed ≥ 1 quantifiable postbaseline PK sample for tislelizumab.

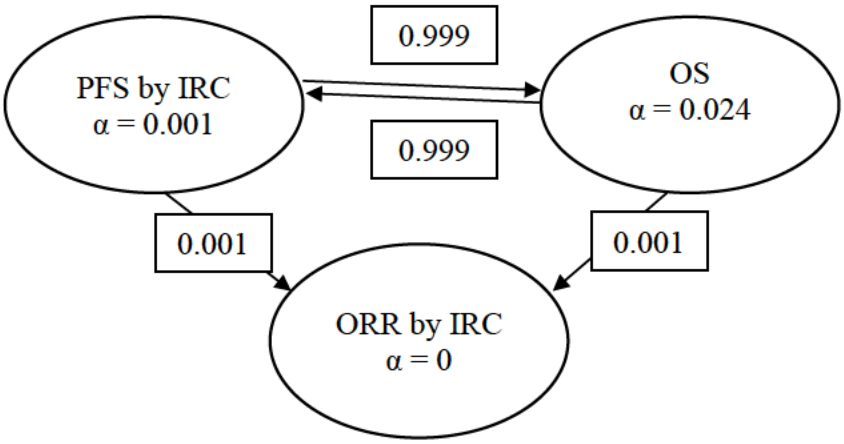
The ADA Analysis Set includes all patients who received ≥ 1 dose of tislelizumab and for whom both baseline ADA and ≥ 1 postbaseline ADA result are available.

9.1.3. Multiplicity

OS and PFS are the dual primary endpoints in this study. The type I error is strongly controlled by initially assigning a 1-sided alpha of 0.001 to the PFS hypothesis and 0.024 to the OS hypothesis. By using the graphic approach of Bretz et al 2009, if the PFS or OS hypotheses are both rejected, the corresponding alpha will be shifted to the hypothesis test of the secondary efficacy endpoint ORR per RECIST v1.1 assessed by the IRC.

Figure 2 shows the initial 1-sided alpha allocation for each hypothesis in the ellipses. The weights for reallocation to other hypothesis tests are represented in boxes on the edges.

Figure 2: Type 1 Error Reallocation Strategy Following Graphical Approach



Abbreviations: IRC, International Review Committee; PFS, progression-free survival; ORR, overall response rate; OS, overall survival

All tests specified in this protocol will be presented in nominal p-values. However, the interpretation must be made with caution, taking the multiplicity issue into consideration.

9.1.4. Patient Disposition

The number of patients who were randomized, treated, discontinued from study drug and/or study, and recorded with important protocol deviations will be counted. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (alive, dead, withdrew consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRFs.

Important protocol deviations will be summarized and listed by category.

9.1.5. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT Analysis Set will be summarized using descriptive statistics.

9.1.6. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report for this protocol.

9.2. Efficacy Analyses

This section describes the statistical methods that address the primary, secondary, and exploratory objectives. All statistical tests, unless otherwise specified, will be conducted in the ITT Analysis Set and stratified for the stratification factors.

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9.2.1. Primary Efficacy Analysis

9.2.1.1. Overall Survival

OS is defined as the time from randomization to death from any cause. The null hypothesis to be tested is:

H_0: OS in Arm A ≤ OS in Arm B

against the alternative:

H_1: OS in Arm A > OS in Arm B

The OS curve will be estimated using the Kaplan-Meier method in the ITT Analysis Set. The difference in the OS curve between the 2 arms is tested using a stratified log-rank test. The 1- sided alpha of 0.024 will be used initially for the testing. The significance level at interim and final analyses will be determined by Lan-DeMets' approximation of the O'Brien Fleming alpha spending function. The hazard ratio of OS will be estimated by a Cox regression model including treatment arm as a factor and prespecified stratification factors as strata.

The median OS and the cumulative probability of OS at every 3 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Landmark OS will be compared between 2 treatment arms for landmark analysis.

If the proportional hazard assumption for OS curves is not valid, the restricted mean survival rate (RMST) analysis for OS may be conducted as the supplementary analysis. In addition, the max combo test may also be applied.

The treatment effect for OS in the absence of subsequent anticancer therapy may be estimated using models, such as the rank preserving structural failure time and the inverse probability of censoring weighting. The choice of model will depend on an examination of the appropriateness of the data to the assumption required by the method.

The primary analysis of OS will treat death due to COVID-19 as an OS event and will be performed regardless of any other COVID-19-related intercurrent events. COVID-19-related sensitivity/supplementary analyses will be specified in the SAP.

Other analyses for emerging intercurrent events for OS may be considered and will be specified in SAP.

9.2.1.2. Progression-free Survival by Independent Review Committee

PFS by IRC is defined as the time from randomization to the first documented disease progression, as assessed by the IRC based on RECIST v1.1, or death from any cause, whichever comes first. The null hypothesis to be tested is:

H_0: PFS by IRC in Arm A ≤ PFS by IRC in Arm B

against the alternative:

H_1: PFS by IRC in Arm A > PFS by IRC in Arm B

The PFS by IRC curve will be estimated using the Kaplan-Meier method in the ITT Analysis Set. The difference in the PFS by IRC curve will be tested using a stratified log-rank test. A

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significance level of 1-sided 0.001 will be used for the testing. The HR of PFS by IRC will be estimated and presented with a 2-sided 95% CI using the same method as that for OS.

The primary and sensitivity censoring rules will follow United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (FDA 2018). The detailed censoring rules will be described in detail in the SAP.

The median PFS and the cumulative probability of PFS at every 3 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. The landmark PFS rates by IRC will be compared between 2 treatment arms for the landmark analysis.

The analyses accounting for nonproportional hazard of PFS by IRC may be carried out as the supplementary analyses when necessary using the same method as of that for OS.

The COVID-19 related sensitivity/supplementary analyses of PFS may be considered and will be specified in the SAP.

9.2.1.3. Sensitivity Analyses for the Primary Endpoints

Sensitivity analyses for OS and PFS by IRC will be conducted to examine the robustness of the statistical methods. In addition to the above specified analyses, post-hoc sensitivity analyses may also be used to address the censoring and missing data problem caused by unanticipated reasons. The details of the sensitivity analyses will be described in the SAP.

9.2.2. Secondary Efficacy Analysis

The PFS by investigators is defined as the time from randomization to the first documented disease progression, as assessed by the investigators based on RECIST v1.1; or death from any cause, whichever comes first. Similar methods as those for the analysis of PFS by IRC will be applied.

DCR by IRC is defined as the proportion of patients whose best overall response (BOR) is CR, PR, or stable disease as determined by the IRC based on RECIST v1.1 in the ITT Analysis Set.

ORR by IRC is defined as the proportion of patients with confirmed objective response (CR or PR), as assessed by IRC based on RECIST v1.1 in the ITT Analysis Set. Patients with no postbaseline response assessment (for any reason) will be considered non-responders.

The null hypotheses of no difference in DCR and ORR by IRC will be tested by a stratified Cochran-Mantel-Haenszel test. The odds ratio and the 2-sided 95% CIs for DCR and ORR will be calculated.

DOR by IRC is defined as the time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, as determined by assessment of the IRC based on RECIST v1.1, or death from any cause, whichever comes first. DOR by IRC will be analyzed similarly to PFS in the patients with objective responses. An unstratified model will be used for the DOR endpoint.

HRQoL is assessed via changes in EORTC QLQ-C30's Global Health Status/Quality of Life, functional and symptom scales and the single item scores, QLQ-LC13’s symptoms scales’ scores and scores of the EQ-5D-5L dimensions scales and Visual Analogue Scale (VAS). Observed

values and changes from baseline will be summarized using descriptive statistics. Clinically meaningful changes postbaseline (percentage of patients with a 10-point improvement or worsening, or to be defined in the SAP) for global health scores and physical function of the QLQ-C30 and dyspnoea, coughing, haemoptysis, peripheral neuropathy, pain in the arms and shoulders, and pain in the chest of LC13 will be calculated by timepoint and compared between the treatment arms using the mixed models which include baseline score, prespecified stratification factors, treatment arm, visit, and treatment arm by visit interaction as fixed effects with visit as a repeated measure with an unstructured covariance structure.

Time to deterioration, defined as worsening scores (10-point change, or to be defined in the SAP if otherwise) of the global health score of QLQ-C30 for 2 consecutive assessments or 1 assessment followed by death from any cause before the next scheduled data collection. Time to deterioration between treatment arms will be compared using a log-rank test, and its Kaplan-Meier probabilities for each arm will be plotted over time.

9.2.3. Exploratory Efficacy Analysis

- ORR by investigators, defined as the proportion of patients with PR or CR as determined by the investigator based on RECIST v1.1
- DOR by investigators, defined as the time from the first occurrence of a documented objective response to the time of the first occurrence of disease progression, as determined by the investigator based on RECIST v1.1, or death from any cause, whichever comes first
- DCR by investigators, defined as the proportion of patients whose BOR is CR, PR, or stable disease based on RECIST v1.1 by investigator

The analytic methods for ORR, DOR and DCR by investigators are the same as those for the analyses of ORR, DOR and DCR by IRC.

9.3. Safety Analyses

Safety will be assessed by the monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Laboratory values, vital signs, ECGs and physical examinations will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively in terms of the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose delays and reductions, dose intensity, and relative dose intensity.

9.3.2. Adverse Events

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment-emergent will be included in summary tables of TEAEs.

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Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class (SOC) and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and preferred term, even if the patient experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to a study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs with ≥ Grade 3 severity, imAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be provided. Descriptive summary for laboratory parameters and their changes from baseline will be calculated.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters and changes from baseline will be presented.

9.4. Pharmacokinetic Analysis

Blood samples for PK analysis of sitravatinib, M10, and tislelizumab will be collected at specified timepoints (Appendix 2). The actual collection date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional timepoints upon sponsor approval to ensure thorough PK monitoring.

For the PK analysis sets that contribute serial plasma samples for sitravatinib and M10 on Cycle 1 Day 1 and Cycle 2 Day 1, plasma concentration-time data of each patient will be tabulated and graphically presented on linear and semilogarithmic scales. Plots of sitravatinib concentration-time data will be presented for Cycle 1 Day 1 (after single dose) and Cycle 2 Day 1 (at steady state). Pharmacokinetic parameters will be determined using a standard noncompartmental method. A listing of patients excluded from the analysis sets and individual data points excluded from the analysis will be provided. The final analysis of PK parameters will be calculated based on actual sample collection times rather than scheduled times. The parameters will be summarized with descriptive statistics (eg, N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] % associated with the geometric mean).

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PK parameters will include, but are not limited to, the following as allowed by data:

C_{max} (ng/mL)	Observed maximum plasma concentration during a sample interval.
C_{τ} (ng/mL)	Observed trough concentration at steady state.

T_{max} (hr)	Observed time to maximum plasma concentration during a sampling interval.
$AUC_{(0-t)}$ (ng•h/mL)	Area under the plasma concentration-time curve from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation.

The sitravatinib, M10, and tislelizumab concentration data collected sparsely at pre-dose and around T_{max} will be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

Additional PK assessments, including population PK analyses, may be conducted as appropriate, and the results of such analyses may be reported separately from the clinical study report.

9.5. Immunogenicity Analyses

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow and reported separately from the main study report.

9.6. Other Exploratory Analyses

9.6.1. Exploratory biomarker analyses

Distribution of PD-L1 expression in TC will be examined. Association between the PD-L1 expression level and efficacy endpoints (OS, PFS, ORR, DOR, and DCR) will be explored. The association between PD-L1 expression and treatment effect will also be examined. The detailed analysis method will be discussed in the SAP.

Analysis of the relationship of response to other exploratory biomarkers (eg, GEP, DNA alteration, tTMB/bTMB, MSI, and ctDNA) may be carried out, depending on the adequacy of available data.

9.7. Sample Size Consideration

The sample size calculation is based on the primary efficacy analysis of OS in the ITT Analysis Set. The hazard ratio of OS is assumed to be 0.70, with a median OS of 14.3 months in the treatment arm and 10.0 months in the comparator arm. The dropout rate for OS is assumed to be 5% per year. A total of 420 patients will be enrolled in a 1:1 randomization over an 18-month period, at a maximum enrollment rate of 28 patients/month and a ramp-up period of 6 months. Approximately 289 OS events are planned for the final analysis, to have a power of 85% with an alpha of 0.024. A group sequential testing of OS will be performed. The hazard ratio assumption of PFS is 0.63 with a median PFS of 5.4 months in the treatment arm and 3.4 months in the control arm. Approximately 332 PFS events are expected to occur at the final analysis of PFS, to have a power of 87% with an alpha of 0.001.

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9.8. Interim Analyses

One interim analysis is planned to occur when approximately 197 of the targeted 289 OS events (68.0%) are documented in the ITT Analysis Set (expected around 22.1 months from the date of first patient randomization if alternative hypothesis is true). Final analysis of PFS will be performed at the time of the interim analysis of OS. No interim analysis of PFS for efficacy is planned.

Stopping boundaries in p-value and z-score for primary analyses of PFS and OS are shown in the Table 17. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, and the revised alpha level due to alpha recycling as described above, using the above prespecified alpha spending function.

Table 17: Stopping Boundaries (in p-value and z-score) of Primary Analysis of Progression-Free Survival and Overall Survival

Endpoint	Analysis	Time (month)	Events (n)	p-value [a] (z-score) for efficacy	Approximate HR threshold
PFS	Final analysis	22.1	332	0.0010	0.712
OS	Interim analysis	22.1	197	< 0.0062 (> 2.50)	0.700
OS	Final analysis	32.5	289	< 0.0221 (> 2.01)	0.789

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
a. One-sided

On the basis of emerging external data, the testing strategy may be modified to improve the efficiency of the design. Should this occur, modifications to the testing strategy will be documented in the SAP before the unblinding of the study.

An early futility analysis based on PFS will be performed, when approximately 48 PFS events were documented in the ITT Analysis Set. The analysis is expected to occur around 8 months from the date of first patient randomization. The non-binding futility boundary is specified at HR = 1.076, as is determined by a Hwang-Shih-DeCani (HSD) beta spending function with parameter 1.

The aim of the interim analysis of efficacy is to determine if there is convincing evidence of outstanding OS and/or PFS benefit. An Independent Data Monitoring Committee (IDMC) will be responsible for making the recommendation regarding stopping the study early based on predefined criteria for OS and/or PFS. More details will be provided in the IDMC charter. Patients will continue to be randomized if enrollment has not been completed and treated per protocol at the time of interim analysis and until a final decision is made by the sponsor after considering the recommendation provided by the IDMC.

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10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Review Committee

An IRC will be established to perform an independent review of all radiologic images for the efficacy analysis and to determine all instances of response and disease progression on the basis of the RECIST v1.1 criteria, in addition to the local investigator review of radiographs. The results from the investigator's review of radiographic images will be used to determine whether patients should be enrolled at Screening and whether patients on study should continue to receive the study drug. The tumor assessments by the IRC will be used for the reporting of the study results.

All decisions made during the performance of the study will be based on the local investigator's assessment of radiographic images, clinical status, and relevant examination of the patients. Sites will submit specific radiographic image files to the centralized data review facility during the study on an ongoing basis or at the sponsor's request. Detailed rules and guidelines for radiographic imaging and tumor assessments by the IRC are outlined separately in the imaging manual and IRC charter.

10.2. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months) and efficacy monitoring will be performed by an IDMC. The first IDMC safety review will occur after ≥ 20 patients have been randomized to study treatment (ie, approximately 10 patients per treatment arm) and have been on treatment for ≥ 1 month in order to determine if the proposed dosing schedule of tislelizumab and sitravatinib combination therapy is safe and tolerable. The IDMC may recommend study modification, including termination of the study, due to safety and/or efficacy concerns. The function and membership of the IDMC will be described in the IDMC charter.

In addition to the planned IDMC review(s), ad hoc reviews may be performed based on new information.

Following IDMC review and discussion, the sponsor will make all final decisions regarding any changes in study conduct. Please see the details in the IDMC charter.

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11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include, but are not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation (ICH) GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

12.3. Study Center Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements specified in the pharmacy manual. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study center will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the pharmacy manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. A patient diary will be provided to each patient in Arm A to record the sitravatinib dose taken each day. Any missed doses with explanations should be recorded in the diary. The diary should be returned to the site personnel for review and will be reviewed by the investigator/study personnel on a regular basis.

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13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug (IND) safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

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13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be reconsented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

13.4. Patient and Data Confidentiality

The principal investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The principal investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the principal investigator and site must ensure that any personal and medical information transmitted to the sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- full dates of birth;
- contact information (such as phone numbers or home or email addresses);
- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;

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- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law. In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the principal investigator and site may provide certain of this personal or medical information to the sponsor or its representatives. Such personal or medical information may not be provided as part of the protocol (eg, as part of the eCRF, or on samples or reports submitted to the central lab).

Investigator and site personnel must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by the sponsor for sharing and transferal of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal or medical information, the principal investigator, site personnel, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

Data generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), the European Medicines Agency (EMA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study that includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

Ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and Ethnicity data are collected in the Clinical Data

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Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM, Implementation Guide v3.2), in accordance with ICH guidance (ICH E5 1998) adopted by the EMA and FDA, to support population PK analysis, which is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications). In some cases, intrinsic or extrinsic factors lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from population PK analyses will be incorporated into drug product labeling to provide guidance on the dose or dosing regimen including any potential dose adjustment in some subpopulations (eg, race or ethnic group). Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators, and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

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14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

14.1.2. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

14.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration given to data protection and medical confidentiality.

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by the lowest level term, preferred term, and primary SOC. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

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14.2. Data Integrity and In-house Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Although the study is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file, and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including but not limited to the following: archival at an off-site facility, or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

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If the investigator cannot guarantee this archiving requirement at the study center for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the Clinical Research Organization managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by your IRB/IEC.

14.4. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to sponsor.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14.5. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2018).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the

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publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.6. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including, but not limited to, those for PK, ADA, and biomarkers) to the assay lab for central lab analysis according to protocol and lab manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to: safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

14.7. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

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If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.5

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment period					End-of-Treatment (EOT) Visit[6]	Safety follow-up phone calls[7]	Survival follow-up
		Cycle 1-2			Cycle 3 and subsequent cycles	Unscheduled visit[5]			
Days (window)	**-28 to -1**	**1[3]**	**8 (± 1)[4]**	**15 (± 2)[4]**	**1 (± 3)**		**30 days (± 7 days) after last dose of study drug**	**60 (± 14 days) and 90 (± 14) days after last dose of tislelizumab**	**Every 3 months (± 14 days)**
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics/medical history/prior medications[2]	X								
Height	X								
Vital signs/weight[8]	X	X	X	X	X	X	X		
Complete physical examination	X						X		
Limited physical examination		X			X				
ECOG performance status	X	X			X	X	X		
12-lead ECG[9]	X	X			X	X	X		
Adverse events[10]	X	X	X	X	X	X	X	X	
Concomitant medications[11]	X	X	X	X	X	X	X	X	
Hematology[12]	X	X[1]	X	X	X	X	X		
Clinical chemistry[12]	X	X[1]	X	X	X	X	X		
Coagulation parameters[12]	X	As clinically indicated					X		
Urinalysis[12]	X	X[1]	As clinically indicated				X		
Pregnancy test[13]	X	X[1]			X	X	X		
Thyroid function[14]	X	Every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc)					X		
HBV/HCV/HIV tests[15]	X	As clinically indicated							
Tumor assessment[16]	X	Every 6 weeks from Cycle 1 Day 1 (± 7 days) (at Weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter							

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Assessment	Screening[1]	Treatment period					End-of-Treatment (EOT) Visit[6]	Safety follow-up phone calls[7]	Survival follow-up
		Cycle 1-2			Cycle 3 and subsequent cycles	Unscheduled visit[5]			
Days (window)	**-28 to -1**	**1[3]**	**8 (± 1)[4]**	**15 (± 2)[4]**	**1 (± 3)**		**30 days (± 7 days) after last dose of study drug**	**60 (± 14 days) and 90 (± 14) days after last dose of tislelizumab**	**Every 3 months (± 14 days)**
Archival tumor tissue[17]	X								
Fresh tumor tissue[18]	X	At the time of confirmed PD							
Sitravatinib administration (Arm A)		Daily							
Tislelizumab administration (Arm A)		X			X				
Docetaxel administration (Arm B)		X			X				
Patient diary		X	X	X	X		X		
Survival status[19]									X
Echocardiogram (preferred) or MUGA[20]	X	Every 12 weeks (± 7 days)							
HRQoL assessment (EORTC-QLQ-C30, QLQ-LC13, EQ-5D-5L)[21]		X (Cycle 1 Day 1). Then every 6 weeks from Cycle 1 Day 1 (± 7 days) (at Weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter to EOT.							
PK sampling for sitravatinib and M10[22]	See Appendix 2								
PK sampling for tislelizumab[22]									
ADA sampling for tislelizumab[22]									
Blood sampling for biomarker analysis[23]		X	Pre-dose on Cycle 3 Day 1 and at the time of confirmed PR/CR (± 14 days), or confirmed PD						

Abbreviations: ADA, antidrug antibody; AE, adverse event; CR, complete response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EGFR, epidermal growth factor receptor; EOT, End-of-Treatment; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level questionnaire; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; GEP, gene expression profiling; HBcAb, hepatitis B core antibody; HBsAb , hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HRQoL, quality of life; imAE, immune-mediated adverse event; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PD, disease progression; PD-L1, programmed cell death ligand-1; PK, pharmacokinetic; PR, partial response; PRO, patient-reported outcomes; QLQ-C30, European Organisation for Research and Treatment of Cancer

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Core Cancer Questionnaire; QLQ-LC13, European Organisation for Research and Treatment of Cancer lung cancer module questionnaire; TT3, serum total triiodothyronine, TT4, serum total thyroxine; TSH, thyroid stimulating hormone; X, to be performed;

Note: On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib should precede tislelizumab infusion.

1. During screening, written informed consent must be signed before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before randomization may be used for screening assessments, rather than repeating such tests. If laboratory tests at screening are performed within 7 days before randomization, these tests (hematology, clinical chemistry, coagulation, urinalysis, and pregnancy test) do not have to be repeated and must be reviewed before the first dose of study drug(s).
2. Includes age or year of birth, gender, self-reported race/ethnicity, smoking history, and drinking history; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history.
3. All assessments on Cycle 2 Day 1 may be performed within a time window of ± 3 days.
4. In Cycle 1 and Cycle 2, all the patients in Arm A will return for assessments on Day 8 and Day 15. Sitravatinib will be given in the clinic.
5. Unscheduled visits may occur any time necessary as per investigator decision or patient's request, for reasons such as assessment or follow-up of AEs. Study activities, as indicated by "X" should be performed based on the reason for the unscheduled visit. If PD is suspected, imaging studies should be performed. The date and reason for an unscheduled visit should be recorded in the eCRF.
6. Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit 30 days (± 7 days) after the last dose of study drug, or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the study drug(s) were initially interrupted due to AEs and then permanently discontinued, the EOT Visit may occur later, but no later than the permitted time of dose delay + 7 days.
7. Telephone contacts (Safety Follow-up phone call) with patients should be conducted to assess imAEs and concomitant medications (if appropriate, eg, associated with an AE or a new anticancer therapy) at 60 days (± 14 days), and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
8. Vital signs collected on study include temperature (°C), pulse, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected while the patient is in a seated or supine position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before; during; and within 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and within 30 minutes after the infusion. Vital signs should also be recorded before administration of sitravatinib; recorded values may be used for pre-tislelizumab assessment if vital signs are collected within 60 minutes before tislelizumab infusion. Docetaxel will follow the same procedure as tislelizumab/sitravatinib.
9. For patients in Arm A, ECG assessments will be performed at pre-dose (within 30 minutes before pre-dose PK sample collection of sitravatinib) and approximately 6 hours post dose (within 30 minutes before post-dose PK sample collection of sitravatinib) on C1D1 and C2D1. For other ECG assessments, when coinciding with blood draws at the same timepoint, ECG assessment should be performed either before blood draws, or at least 30 minutes after blood draws. Patients should rest in semi-recumbent supine position for ≥ 10 minutes before each ECG collection. If an ECG has been performed within 7 days before randomization (for patients in Arm B) or before the EOT visit (for all patients), the test does not need to be repeated on Cycle 1 Day 1, and the EOT visit, respectively. ECG collection may be done at other timepoints as clinically indicated.
10. AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0.
11. All concomitant medications received within 30 days before the first dose of study drug should be recorded.

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12. Hematology and clinical chemistry will be performed at each cycle for both arms. Additional laboratory tests are required weekly for patients in Arm A in Cycle 1 and Cycle 2. After Cycle 1, laboratory tests can be performed up to 2 days before Day 1 of subsequent cycles, and results are to be reviewed within 48 hours before study drug administration. Coagulation tests as specified in Appendix 3 are required at screening and subsequently as clinically indicated. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. Urinalysis will be performed on Cycle 1 Day 1 (if not done within 7 days before the randomization) and subsequently as clinically indicated.
13. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days before randomization. Urine or serum pregnancy tests will be performed during treatment, and at the EOT Visit. A negative pregnancy test must be completed and recorded before administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
14. Thyroid function tests for FT3, FT4, and TSH will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the EOT Visit. If test for FT3 or FT4 is not available, TT3 or TT4 should be tested instead.
15. Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). Viral load assessment (HBV DNA and HCV RNA) will be performed if the HBsAg and/or HCV antibody test is positive. HIV serology is required at screening for patients in Germany with an unknown HIV status and will include antigen and/or antibodies. Viral load assessment (HIV RNA) and CD4+ T-cell count tests will be conducted at screening for patients outside Germany with a known HIV infection.
16. Tumor imaging will be performed within 28 days before randomization and while on study, approximately every 6 weeks ± 7 days from Cycle 1 Day 1 in the first 12 months and approximately every 9 weeks ± 7 days thereafter. All measurable and nonmeasurable lesions should be assessed and documented; Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments. Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a complete response (CR) is suspected in target lesion or when progression in bone is suspected. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. The same imaging technique should be used throughout the study for each patient. After the first documentation of response (CR or PR), confirmation of tumor response should occur ≥ 4 weeks after the first response or at the next scheduled assessment timepoint (see Section 7.5 for details).
17. Archival tumor tissues (FFPE blocks or approximately 15 [at least 5 slides for PD-L1 assessment] freshly cut unstained FFPE slides from each block) must be collected (if available) for biomarker analysis to assess PD-L1 expression (mandatory) and, if tissue samples are sufficient, to assess biomarkers such as GEP, DNA alteration, tTMB and MSI (optional). Tissues for optional biomarker analysis can be retrospectively provided after relative regulation approval, eg HGRAC (Regulations on Management of Human Genetic Resources of the People's Republic of China). Submission of < 15 unstained slides is not a protocol deviation. If no archival tumor tissues can be provided, a fresh biopsy is mandatory during Screening for PD-L1 assessment. For nonsquamous NSCLC, documentation of *EGFR* status with no sensitizing mutation by tissue-based test must be provided prior enrollment. For undocumented cases, additional archival or fresh biopsy tumor tissues (FFPE blocks or approximately 3 freshly cut unstained FFPE slides from each block) will be required for central assessment of *EGFR* mutation status during the screening period. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include core needle biopsies for non-superficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration, brushing, cell pellets from pleural effusion, ~~and~~ lavage samples, and bone/bone marrow aspirates are not acceptable. Written patient consent is required for fresh tumor biopsies.
18. In addition to archival tumor tissues, fresh biopsies from an accessible tumor site(s) at screening (within 28 days before randomization) and/or at the time of confirmed PD are recommended to explore response or resistance mechanisms. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy.

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19. Information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the EOT, or as directed by the sponsor until death, lost to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed up for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
20. Evaluations of cardiac function will be performed at screening and every 12 weeks (± 7 days). Evaluation by echocardiogram is preferred. Evaluation by MUGA scan is an acceptable alternative, if necessary. The method used for individual patients should be consistent throughout study participation.
21. EORTC-QLQ-C30, QLQ-LC13 and EQ-5D-5L should always be completed before other assessments performed during a visit and drug administration. PROs are to be completed at baseline (Cycle 1 Day 1), then every 6 weeks from Cycle 1 Day 1 (± 7 days) (at weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter to EOT. If the disease evaluation does not coincide with a clinic visit, the assessment of PRO should be completed at the clinic visit closest to the disease evaluation.
22. See Appendix 2 for schedule of PK sampling for sitravatinib and M10, PK sampling for tislelizumab, and ADA sampling for tislelizumab.
23. Peripheral blood samples will be collected for biomarker assessments, such as DNA alteration, bTMB, MSI and ctDNA. Approximately 10 mL of peripheral blood samples will be collected at baseline (pre-dose on Cycle 1 Day 1) and pre-dose on Cycle 3 Day 1. For patients who have confirmed CR/PR (± 14 days) or confirmed PD, additional blood samples (approximately 10 mL) will be collected upon each confirmation. Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual. Written patient consent is required for blood sample collections.

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APPENDIX 2. SCHEDULE OF PHARMACOKINETICS/ ANTIDRUG ANTIBODY ASSESSMENTS

Sitravatinib and M10 PK (Only for patient from Arm A)[a]

	Day 1 of Cycle 1 and Cycle 2									Day 1 of Cycle 5		Day 1 of Cycle 9	Day 1 of Cycle 17
Collection Time Allowable Window [b]	Pre-dose -30min [c]	0.5hr ±10min	1hr ±10min	2hr ±15min	4hr ±20min	6hr ±20min	8hr ±30min	10hr ±1hr	12hr [d] ±2hr	Pre-dose -30min [c]	6hr ±20min	Pre-dose -30min [c]	Pre-dose -30min [c]
12 patients Serial PK sampling [e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Other patients Sparse PK sampling	X					X				X	X	X	X

Abbreviations: hr, hour; min, minutes; PK, pharmacokinetic; X, to be performed

[a] One blood sample will be collected at each timepoint for sitravatinib and M10 analysis.

[b] An additional PK blood sample may be drawn before a daily sitravatinib dose (trough sample) in any of the following events: 1) as soon as possible after a serious adverse event, 2) at a clinic visit ≥ 1 week following a dose modification of sitravatinib.

[c] Within 30 minutes before administration of Sitravatinib.

[d] Post-dose samples for sitravatinib at 12 hr is optional and is dependent upon site feasibility.

[e] 6 patients enrolled (if applicable) from China sites and 6 patients enrolled (if applicable) from ex-China sites.

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Tislelizumab PK/ADA (Only for patients from Arm A)

	Day 1 of Cycle 1, 2, 5, 9, 17 (if achieved)		EOT Visit
Collection time and allowable window[a]	**Pre-tislelizumab infusion - 30 min[b]**	**Post-tislelizumab infusion + 30 min[c]**	**30 (± 7) days after last dose**
Sparse PK sampling	X	X (Cycle 1 Day 1 and Cycle 5 Day 1 only)	X
ADA sampling	X		X

Abbreviations: ADA, antidrug antibody; EOT, End-of-Treatment; imAE, immune-mediated adverse event; PK, pharmacokinetic; X, to be performed

[a] Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab.

[b] Within 30 minutes before starting infusion of tislelizumab

[c] Within 30 minutes after completing the tislelizumab infusion

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APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Serum chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium [a] Creatinine Glucose Lactate dehydrogenase Total protein Creatine kinase [b] CK-MB [b]	Hematocrit Hemoglobin Platelet counts WBC count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Glucose Protein [c] Blood

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; WBC, white blood cell.

[a] Total calcium values will be corrected for patients with hypoproteinemia.

[b] All patients will undergo a creatine kinase and CK-MB testing at screening, and the tests are to be repeated at all scheduled visits during the first 3 treatment cycles, all pre-dose assessments from Cycle 4 onwards, and at the End-of-Treatment. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[c] If urinary protein by dipstick is ≥ 2+, then 24-hour urinary protein.

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al 1982. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

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APPENDIX 5. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al 2009.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical exam (when superficial)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all nonmeasurable.

Bone lesions:

- Bone scan, positron-emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

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Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- The concept of cystic metastases also applies to metastatic lesions with a necrotic component. Hence, measurable lesions with a necrotic component may be selected as target lesions. However, if non-necrotic lesions are present, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. A maximum of 2 measurable lymph nodes, inclusive of all lymphatic chains involved, may be chosen as target lesions (ie, the lymphatic system is considered one organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), how representative they are of all involved organs, and whether they lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 perpendicular dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal, but the axial plane is recommended for measurements). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm by 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal

progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). If a nontarget lymph node normalizes (< 10 mm in short axis) after baseline, the respective evaluation should be "absent."

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: Target lesion measurements should be performed in the axial plane. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans). If there is a change from CT to MRI or the reverse, target lesions should continue to be measured provided the imaging parameters do not render measurements incomparable.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response (CR) or surgical resection is an endpoint.

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- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial Response (PR): ≥ a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): ≥ a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. (Note: The appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Both PR and PD: If the change in sum of diameters is consistent with both PR and PD at a tumor assessment visit, PD should take precedence.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target nodal lesions recorded in a separate section where, to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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- Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
  When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of 1 or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of

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overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only nonmeasurable disease: This circumstance arises in some phase 3 studies when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or it may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he or she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

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- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response
- It is assumed that at each protocol specified timepoint, a response assessment occurs. The following table provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline:

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

When patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	SD (Non-CR/non-PD)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; SD, stable disease.

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Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best

response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known.

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered non-evaluable.

Best response determination in studies where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In studies where confirmation of response is required, repeated "NE" (not evaluable) timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Conditions that define "early progression, early death, and inevaluability" are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of

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FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

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Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, ie, in randomized studies (phase 2 or 3) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice.

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However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

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APPENDIX 6. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barré syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
Lambert-Eaton myasthenic syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome
Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

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APPENDIX 7. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin et al 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

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APPENDIX 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-mediated adverse event (imAE) are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the AE?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-mediated Adverse Events

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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Recommended Diagnostic Tests in the Management of Possible Immune-mediated Adverse Events

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

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Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required.
- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF]).
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Colitis/Diarrhea	**1** Mild symptoms: ≤ 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. • If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.

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Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myocarditis[a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune related, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.
[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

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APPENDIX 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2009) and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

This CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) is reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black]

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here:
https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

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APPENDIX 10. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical studies include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)
  Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and if used, this method must be used in combination with one of the highly effective forms of birth control listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, “women of no childbearing potential” are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone (FSH) concentration > 30 mIU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group (CTFG) 2014.

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Appendix 11. Medications Or Substances to Be Avoided or Used With Caution During Treatment With Study Drugs

Examples of Drugs with a Known Risk of Torsades de Pointes

Aclarubicin (Only on Non-US Market)	Cocaine	Hydroxychloroquine	Probucol (Removed from US Market)
Amiodarone	Disopyramide	Ibogaine (Only on Non-US Market)	Procainamide
Anagrelide	Dofetilide	Ibutilide	Propofol
Arsenic trioxide	Domperidone (Only on Non-US Market)	Levofloxacin	Quinidine
Astemizole (Removed from US Market)	Donepezil	Levomepromazine (Methotrimeprazine) (Only on Non-US Market)	Roxithromycin (Only on Non-US Market)
Azithromycin	Dronedarone	Levomethadyl acetate (Removed from US Market)	Sevoflurane
Bepridil	Droperidol	Levosulpiride (Only on Non-US Market)	Sotalol
Cesium Chloride	Erythromycin	Mesoridazine (Removed from US Market)	Sparfloxacin (Removed from US Market)
Chloroquine	Escitalopram	Methadone	Sulpiride (Only on Non-US Market)
Chlorpromazine	Flecainide	Moxifloxacin	Sultopride (Only on Non-US Market)
Chlorprothixene (Only on Non-US Market)	Fluconazole	Nifekalant (Only on Non-US Market)	Terfenadine (Removed from US Market)
Cilostazol	Gatifloxacin (Removed from US Market)	Ondansetron	Terlipressin (Only on Non-US Market)
Ciprofloxacin	Grepafloxacin (Removed from US Market)	Oxaliplatin	Terodiline (Only on Non-US Market)
Cisapride (Removed from US Market)	Halofantrine (Only on Non-US Market)	Papaverine HCl (Intra-coronary)	Thioridazine
Citalopram	Haloperidol	Pentamidine	Vandetanib
Clarithromycin	Hydroquinidine (Dihydroquinidine) (Only on Non-US Market)	Pimozide	

* Woosley RL, Heise CW, Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [Accession Date: 10 April 2020], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755; for the most current information, access the website: www.CredibleMeds.org.

Examples of Drugs with Conditional Risk of Torsades de Pointes

Abiraterone	Eperisone (Only on Non-US Market)	Ketoconazole	Propafenone

Amantadine	Esomeprazole	Lansoprazole	Quetiapine
Amisulpride	Famotidine	Loperamide	Quinine sulfate
Amitriptyline	Fluoxetine	Metoclopramide	Ranolazine
Amphotericin B	Fluvoxamine	Metolazone	Risperidone
Amsacrine (Acridinyl anisidide) (Only on Non-US Market)	Furosemide (frusemide)	Metronidazole	Sertraline
Atazanavir	Galantamine	Nelfinavir	Solifenacin
Bendroflumethiazide (Bendrofluazide)	Garenoxacin (Only on Non-US Market)	Olanzapine	Telaprevir
Chloral hydrate	Hydrochlorothiazide	Omeprazole	Torsemide (Torasemide)
Cimetidine	Hydroxyzine	Pantoprazole	Trazodone
Clomipramine	Indapamide	Paroxetine	Voriconazole
Diphenhydramine	Itraconazole	Piperacillin/Tazobactam	Ziprasidone
Doxepin	Ivabradine	Posaconazole	

* Woosley RL, Heise CW, Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [Accession Date: 10 April 2020], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755; for the most current information, access the website: www.CredibleMeds.org.

Examples of Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP transporters

Transporter	**Substrates**
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan.
BCRP	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.

Abbreviations: BCRP, breast cancer resistance protein; P-gp, P-glycoprotein

Exmples of Sensitive Substrates and Substrates with Narrow Therapeutic Index for the indicated CYP Enzymes

Enzyme	**Substrates**
CYP2C8	Repaglinide.
CYP2C9	Celecoxib
CYP2C19	S-mephenytoin, omeprazole

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CYP2D6	Atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine.
CYP3A	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil.

Examples of Inhibitors of CYP3A4 or P-gp.

Strong CYP3A4 Inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, tipranavir/ritonavir, troleandomycin, voriconazole.
Moderate CYP3A4 Inhibitors	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil.
P-gp Inhibitors	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

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Appendix 12. European Organisation For Research And Treatment Of Cancer Quality Of Life Cancer Questionnaire QLQ-C30

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ __ __ __ __
Today's date (Day, Month, Year): 31 __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

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During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

APPENDIX 13. European Organisation For Research And Treatment Of Cancer Quality Of Life Questionnaire Lung Cancer QLQ-LC13

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EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 14. The 5-Level Version Of European Quality Of Life 5-Dimensional Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

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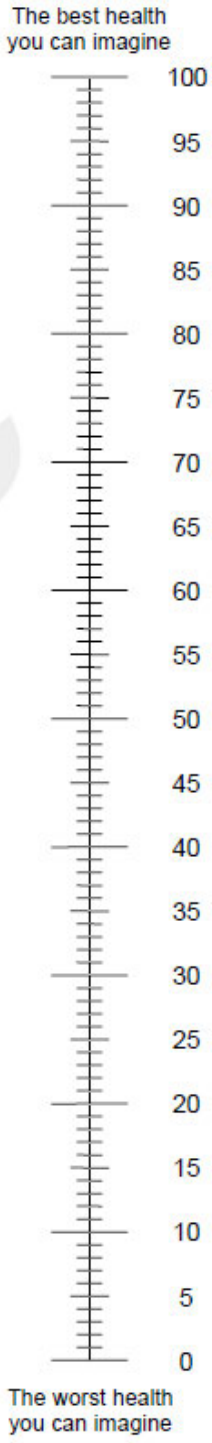
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample